

MATERIALS AND METHODS FOR THE TREATMENT OF DIABETES,  
5 HYPERLIPIDEMIA, HYPERCHOLESTEROLEMIA, AND ATHEROSCLEROSIS

This application is a Divisional application of U.S. patent application 09/841,351, filed April 24, 2001, which claims the benefit of United States Provisional Applications 60/199,146, filed April 24, 2000 and 60/281,982, filed April 6, 2001, the disclosures of which are each incorporated by reference in their entireties, including all figures, tables, and chemical structures.

Diabetes is one of the most prevalent chronic disorders worldwide with significant personal and financial costs for patients and their families, as well as for society. Different types of diabetes exist with distinct etiologies and pathogeneses. For example, diabetes mellitus is a disorder of carbohydrate metabolism, characterized by hyperglycemia and glycosuria and resulting from inadequate production or utilization of insulin.

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For people with Type II diabetes, insulin secretion is often enhanced, presumably to compensate for insulin resistance. Eventually, however, the B-cells fail to maintain sufficient insulin secretion to compensate for the insulin resistance. Mechanisms responsible for the B-cell failure have not been identified, but may be related to the chronic demands placed on the B-cells by peripheral insulin resistance and/or to the effects of hyperglycemia. The B-cell failure could also occur as an independent, inherent defect in "pre-diabetic" individuals.

NIDDM often develops from certain at risk populations. One such population is individuals with polycystic ovary syndrome (PCOS). PCOS is the most common endocrine disorder in women of reproductive age. This syndrome is characterized by hyperandrogenism and disordered gonadotropin secretion producing oligo- or anovulation. Recent prevalence estimates suggest that 5-10% of women between 18-44 years of age (about 5 million women, according to the 1990 census) have the full-blown syndrome of hyperandrogenism, chronic anovulation, and polycystic ovaries. Despite more than 50 years since its original description, the etiology of the syndrome remains unclear. The biochemical profile, ovarian morphology, and clinical features are non-specific; hence, the diagnosis remains one of exclusion of disorders, such as androgen-secreting tumors, Cushing's Syndrome, and late-onset congenital adrenal hyperplasia. PCOS is associated with profound insulin resistance resulting in substantial hyperinsulinemia. As a result of their insulin resistance, PCOS women are at increased risk to develop NIDDM.

NIDDM also develops from the at risk population of individuals with gestational diabetes mellitus (GDM). Pregnancy normally is associated with progressive resistance to insulin-mediated glucose disposal. In fact, insulin sensitivity is lower during late pregnancy than in nearly all other physiological conditions. The insulin resistance is thought to be mediated in large part by the effects of circulating hormones such as placental lactogen, progesterone, and cortisol, all of which are elevated during pregnancy. In the face of the insulin resistance, pancreatic B-cell responsiveness to glucose normally increases nearly 3-fold by late pregnancy, a response that serves to minimize the effect of insulin resistance on circulating glucose levels. Thus, pregnancy provides a major "stress-test" of the capacity for B-cells to compensate for insulin resistance.

Other populations thought to be at risk for developing NIDDM include persons with Syndrome X; persons with concomitant hyperinsulinemia; persons with insulin resistance characterized by hyperinsulinemia and by failure to respond to exogenous insulin; and persons with abnormal insulin and/or evidence of glucose disorders associated with excess circulating glucocorticoids, growth hormone, catecholamines, glucagon, parathyroid hormone, and other insulin-resistant conditions.

Failure to treat NIDDM can result in mortality due to cardiovascular disease and in other diabetic complications including retinopathy, nephropathy, and peripheral neuropathy. There is a substantial need for a method of treating at risk populations such as those with PCOS and GDM in order to prevent or delay the onset of NIDDM thereby bringing relief of symptoms, improving the quality of life, preventing acute and long-term complications, reducing mortality and treating accompanying disorders of the populations at risk for NIDDM.

For many years, treatment of NIDDM has involved a program aimed at lowering blood sugar with a combination of diet and exercise. Alternatively, treatment of NIDDM can involve oral hypoglycemic agents, such as sulfonylureas alone or in combination with insulin injections. Recently, alpha-glucosidase inhibitors, such as acarbose, have been shown to be effective in reducing the postprandial rise in blood glucose (Lefevre, et al., *Drugs* 1992; 44:29-38). In Europe and Canada another treatment used primarily in obese diabetics is metformin, a biguanide.

Compounds useful in the treatment of the various disorders discussed above, and methods of making the compounds, are known and some of these are disclosed in U.S. Pat. Nos. 5,223,522 issued Jun. 29, 1993; 5,132,317 issued Jul. 12, 1992; 5,120,754 issued Jun. 9, 1992; 5,061,717 issued Oct. 29, 1991; 4,897,405 issued Jan. 30, 1990; 4,873,255 issued Oct. 10, 1989; 4,687,777 issued Aug. 18, 1987; 4,572,912 issued Feb. 25, 1986; 4,287,200 issued Sep. 1, 1981; 5,002,953, issued Mar. 26, 1991; U.S. Pat. Nos. 4,340,605; 4,438,141; 4,444,779; 4,461,902; 4,703,052; 4,725,610; 4,897,393; 4,918,091; 4,948,900; 5,194,443; 5,232,925; and 5,260,445; WO 91/07107; WO 92/02520; WO 94/01433; WO 89/08651; and JP Kokai 69383/92. The compounds disclosed in these issued patents and applications are useful as therapeutic agents for the treatment of diabetes, hyperglycemia, hypercholesterolemia, and

hyperlipidemia. The teachings of these issued patents are incorporated herein by reference in their entireties.

Drug toxicity is an important consideration in the treatment of humans and animals. Toxic side effects resulting from the administration of drugs include a variety of conditions that range from low-grade fever to death. Drug therapy is justified only when the benefits of the treatment protocol outweigh the potential risks associated with the treatment. The factors balanced by the practitioner include the qualitative and quantitative impact of the drug to be used as well as the resulting outcome if the drug is not provided to the individual. Other factors considered include the physical condition of the patient, the disease stage and its history of progression, and any known adverse effects associated with a drug.

Drug elimination is typically the result of metabolic activity upon the drug and the subsequent excretion of the drug from the body. Metabolic activity can take place within the vascular supply and/or within cellular compartments or organs. The liver is a principal site of drug metabolism. The metabolic process can be categorized into synthetic and nonsynthetic reactions. In nonsynthetic reactions, the drug is chemically altered by oxidation, reduction, hydrolysis, or any combination of the aforementioned processes. These processes are collectively referred to as Phase I reactions.

In Phase II reactions, also known as synthetic reactions or conjugations, the parent drug, or intermediate metabolites thereof, are combined with endogenous substrates to yield an addition or conjugation product. Metabolites formed in synthetic reactions are, typically, more polar and biologically inactive. As a result, these metabolites are more easily excreted via the kidneys (in urine) or the liver (in bile). Synthetic reactions include glucuronidation, amino acid conjugation, acetylation, sulfoconjugation, and methylation.

One of the drugs used to treat Type II diabetes is troglitazone. The major side effects of troglitazone are nausea, peripheral edema, and abnormal liver function. Other reported adverse events include dyspnea, headache, thirst, gastrointestinal distress, insomnia, dizziness, incoordination, confusion, fatigue, pruritus, rash, alterations in blood cell counts, changes in serum lipids, acute renal insufficiency, and dryness of the mouth. Additional symptoms that have been reported, for which the relationship to troglitazone is unknown, include palpitations, sensations of hot and

cold, swelling of body parts, skin eruption, stroke, and hyperglycemia. Accordingly, forms of glitazones which have fewer, or no, adverse effects (i.e., less toxicity) are desirable.

5 The principal difference between the compounds of the present invention and related compounds is the presence of a carboxyl group, either OOC- or COO-, directly attached to the 4-position of the phenyl ring. In the literature, thiazolidinediones having similar therapeutic properties have an ether function at the 4-position of the phenyl ring instead of a carboxyl group.

10 The presence of the carboxyl group has significant consequences for the biological behavior of these new compounds. The present compounds are primarily metabolized by hydrolytic enzymatic systems, whereas compounds having an ether function are metabolized only by oxidative enzymes. Hydrolytic enzymatic systems are ubiquitous, non-oxidative, not easily saturable, and non-inducible, and, therefore, reliable. By contrast, oxidative systems are mediated by the P-450 isozymes. These  
15 systems are localized, mainly, in the liver, saturable and inducible (even at low concentrations of therapeutic compounds) and therefore are highly unreliable.

The compounds of the subject invention do not rely on saturable hepatic systems for their metabolism and elimination, whereas the prior art compounds exert a heavy bio-burden on hepatic functions, especially in the presence of other drugs that  
20 rely on similar enzymes for detoxification. Thus, the present compounds have a much more desirable toxicity profile than prior art compounds, especially when considering liver toxicity and potentially fatal drug-drug interactions.

Upon metabolism by plasma and tissue esterases, the compounds of this invention are hydrolyzed into 2 types of molecules: 1) an alcohol or a phenol, and 2) a  
25 carboxylic acid. Therefore, any compound that yields compound 1, compound 2, compound 3, or compound 4, as defined in Table I, as a primary metabolite falls under the definition of this invention. This concept is illustrated in Figure 1, taking compound 9 (of Table I) and compound 145 (of Table X) as specific examples of compounds giving 1 and 3, respectively, upon non-oxidative metabolism by esterases.

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Brief Summary of the Invention

5 The subject invention provides materials and methods for the safe and effective treatment of diabetes, hyperlipidemia, hypercholesterolemia, and atherosclerosis. In a preferred embodiment, the subject invention provides therapeutic compounds for the treatment of diabetes. The compounds of the subject invention can be used to treat at-risk populations, such as those with PCOS and GDM, in order to prevent or delay the onset of NIDDM thereby bringing relief of symptoms, improving the quality of life, preventing acute and long-term complications, reducing mortality and treating accompanying disorders.

10 Advantageously, the subject invention provides compounds that are readily metabolized by the physiological metabolic drug detoxification systems. Specifically, in a preferred embodiment, the therapeutic compounds of the subject invention contain an ester group, which does not detract from the ability of these compounds to provide a therapeutic benefit, but which makes these compounds more susceptible to degradation by hydrolases, particularly serum and/or cytosolic esterases. The subject invention further provides methods of treatment comprising the administration of these compounds to individuals in need of treatment for Type II diabetes, hyperlipidemia, hypercholesterolemia, and atherosclerosis.

20 In a further embodiment, the subject invention pertains to the breakdown products that are formed when the therapeutic compounds of the subject invention are acted upon by esterases. These breakdown products can be used as described herein to monitor the clearance of the therapeutic compounds from a patient.

25 In yet a further embodiment, the subject invention provides methods for synthesizing the therapeutic compounds of the subject invention.

### Brief Description of the Figures

Figure 1 depicts exemplary metabolic breakdown products resulting from the  
5 actions of esterases on compounds of the invention.

Figures 2-3 provide an exemplary synthetic scheme for compounds 1 through  
4 (of Table I). These compounds can be conveniently prepared by the Knoevenagel  
reaction between an aldehyde and thiazolidine-2,4-dione using, for example, sodium  
10 acetate in acetic anhydride, or piperidine and benzoic acid in methylene chloride as a  
reaction medium.

Figure 4 illustrates an alternative reaction scheme for the production of  
compound 1 (of Table I). In this reaction scheme, *para*-anisidine undergoes a  
15 diazotation reaction with sodium nitrite and hydrochloric acid. The diazonium  
chloride salt undergoing, in turn, a radicalar reaction with methyl acrylate and then a  
cyclization reaction with thiourea, the product of which is hydrolyzed to the  
thiazolidinedione molecule.

Figure 5 shows an exemplary synthetic scheme for the compounds described  
20 in Table I (compounds 5 to 32). These compounds can be made via an esterification  
reaction between 1 or 2 and an appropriately substituted carboxylic acid, or between 3  
or 4 and an appropriately substituted alcohol.

Figure 6 depicts the synthesis of the 4-oxazoleacetic acid and the 4-  
25 oxazoleethanol moiety starting from aspartic acid derivatives in which R<sub>2</sub> and R<sub>3</sub> are  
methyl or hydrogen.

Figure 7 describes the synthesis of the 4-oxazolecarboxylic acid and 4-  
30 oxazolemethanol groups. The synthesis starts from ethyl acetoacetate in which a 2-  
amino-group is introduced via oxime formation followed by reduction with zinc  
powder. The synthesis then proceeds as before, where the R<sub>1</sub> group is introduced by

acylating the amino group, followed by cyclization with sulfuric acid in ethyl acetate, and finally ester cleavage or reduction to the alcohol.

Figure 8 shows how steric hindrance can be introduced under the form of methyl groups on the 4-methanol moiety. Starting from pentane-2,4-dione and following the same synthetic sequence as in Figure 7 leads to the 4-acetyloxazole compounds which can be reduced by sodium borohydride to the 4-(1-ethyl)oxazole, or which can be transformed to 4-(2-hydroxy-2-propyl) oxazole with a methyl Grignard reagent such as methyl magnesium iodide.

Figure 9 illustrates an alternative synthetic scheme wherein condensation of a thioamide with methyl 4-bromo-3-oxopentanoate gives methyl 4-thiazoleacetate. Ester cleavage with lithium hydroxide or reduction with lithium aluminum hydride gives the corresponding acid or the alcohol, respectively.

Figures 10-17 depict the synthesis of compounds **105** to **224** in Tables VI to XVII. These compounds contain an amino acid or an amino alcohol as part of their structure.

Figure 18 provides an exemplary synthetic pathway for compounds **225** to **242** (Table XVIII). These compounds are oxazoline-4-carboxylic acid types of compounds. Their synthesis (Figure 18) starts from serine ( $R_5=H$ ) or from threonine ( $R_5=CH_3$ ) benzyl ester. The ester is coupled with an alkyl or an arylcarboxylic acid using for example EDC as a coupling agent. The serine or threonine group then cyclizes into an oxazoline upon treatment with thionyl chloride. Coupling with 5-(4-hydroxybenzyl)thiazolidine-2,4-dione using DCC/DMAP/methylene chloride gives compounds **225** to **242**.

Figures 19-20 illustrate the activity of representative compounds on serum glucose and insulin levels in non-insulin dependent diabetic mellitus (NIDDM) KK-A<sup>y</sup> male mice. Post-treatment data for each group were transferred to a percentage of pretreatment values and unpaired Student's t test was used for comparison between vehicle and test substance treated groups. Results show a significant reduction of



both serum glucose and serum insulin relative to the vehicle control group. Reduction in serum glucose and serum insulin levels were comparable to the reduction observed in the troglitazone-treated animals. The results are also presented in Table XXI.

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#### Brief Description of the Tables

Tables I-XXII depict exemplary compounds according to the invention. The term "db" indicates a double bond between P and Q.

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Table XXIII illustrates the effects of exemplary compounds on serum glucose and insulin levels in NIDDM mice.

#### Detailed Disclosure of the Invention

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The subject invention provides materials and methods for the treatment of non-insulin dependent diabetes mellitus (NIDDM), hyperlipidemia, hypercholesterolemia, and atherosclerosis. Advantageously, the therapeutic compounds of the subject invention are stable in storage but have a shorter half-life in the physiological environment than other drugs which are available for treatment of diabetes; therefore, the compounds of the subject invention can be used with a lower incidence of side effects and toxicity, especially in patients having elevated liver function or compromised liver function.

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In a preferred embodiment of the subject invention, therapeutic compounds are provided which are useful in the treatment of diabetes, hyperlipidemia, hypercholesterolemia, and atherosclerosis and which contain an ester group which is acted upon by esterases thereby breaking down the compound and facilitating its efficient removal from the treated individual. In a preferred embodiment the therapeutic compounds are metabolized by the Phase I drug detoxification system and are exemplified by the compound of Formula I.

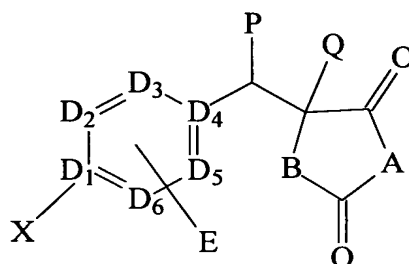
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The compounds of Formula I can be generally described as 5-benzyl- or 5-benzylidene-thiazolidine-2,4-dione compounds having a carboxyl group directly attached to the *para*-position of the phenyl ring. These compounds represent a new

class of chemical compounds having therapeutic properties for the treatment of type-II diabetes mellitus, atherosclerosis, hypercholesterolemia, and hyperlipidemia.

Formula I



For compounds of Formula I:

A and B may be the same or different and are C, N, NO, NH, SO<sub>0-2</sub>, O;

D<sub>1</sub>-D<sub>6</sub> can be the same or different and are C, N, S, or O;

E can be attached to one or more of the atoms located at D<sub>1</sub>-D<sub>6</sub>;

P and Q can be a double bond; or

P, Q, and E can be the same or different and are a moiety selected from the group consisting of H, C<sub>1-10</sub> alkyl, substituted alkyl groups, substituted or unsubstituted carboxylic acids, substituted or unsubstituted carboxylic esters, halogen, carboxyl, hydroxyl, phosphate, phosphonate, aryl, CN, OH, COOH, NO<sub>2</sub>, NH<sub>2</sub>, SO<sub>2-4</sub>, C<sub>1-20</sub> heteroalkyl, C<sub>2-20</sub> alkenyl, alkynyl, alkynyl-aryl, alkynyl-heteroaryl, aryl, C<sub>1-20</sub> alkyl-aryl, C<sub>2-20</sub> alkenyl-aryl, heteroaryl, C<sub>1-20</sub> alkyl-heteroaryl, C<sub>2-20</sub> alkenyl-heteroaryl, cycloalkyl, heterocycloalkyl, C<sub>1-20</sub> alkyl-heterocycloalkyl, and C<sub>1-20</sub> alkyl-cycloalkyl, any of which may be, optionally, substituted with a moiety selected from the group consisting of C<sub>1-6</sub> alkyl, halogen, OH, NH<sub>2</sub>, CN, NO<sub>2</sub>, COOH, or SO<sub>2-4</sub>. Exemplary heterocyclic groups include, but not limited to, morpholine, triazole, imidazole, pyrrolidine, piperidine, piperazine, pyrrole, dihydropyridine, aziridine, thiazolidine, thiazoline, thiadiazolidine or thiadiazoline.

Substituted carboxylic acids, substituted carboxylic esters, and substituted alkyl groups can be substituted at any available position with a moiety selected from the group consisting of C<sub>1-10</sub> alkyl, halogen, CN, OH, COOH, NO<sub>2</sub>, NH<sub>2</sub>, SO<sub>2-4</sub>, C<sub>1-20</sub> heteroalkyl, C<sub>2-20</sub> alkenyl, alkynyl, alkynyl-aryl, alkynyl-heteroaryl, aryl, C<sub>1-20</sub> alkyl-aryl, C<sub>2-20</sub> alkenyl-aryl, heteroaryl, C<sub>1-20</sub> alkyl-heteroaryl, C<sub>2-20</sub> alkenyl-heteroaryl, cycloalkyl, heterocycloalkyl, C<sub>1-20</sub> alkyl-heterocycloalkyl, and C<sub>1-20</sub> alkyl-cycloalkyl,

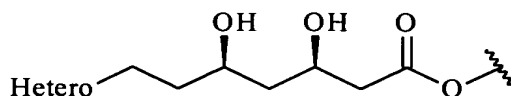
any of which may be, optionally, substituted with a moiety selected from the group consisting of C<sub>1-6</sub> alkyl, halogen, OH, NH<sub>2</sub>, CN, NO<sub>2</sub>, COOH, or SO<sub>2-4</sub>. Exemplary heterocyclic groups include, but are not limited to, morpholine, triazole, imidazole, pyrrolidine, piperidine, piperazine, pyrrole, dihydropyridine, aziridine, thiazolidine, thiazoline, thiadiazolidine, and thiadiazoline.

X is -OH, -COOH, or a substituted carboxylic group having the carboxyl moiety OOC- or COO- directly attached to the phenyl ring of the compound of Formula 1. The carboxylic acid group can be substituted with a moiety selected from the group consisting of alkyloxycarbonyl, alkylcarbonyloxy, aryloxycarbonyl, arylcarbonyloxy, heteroalkyloxycarbonyl, heteroalkylcarbonyloxy, heteroaryloxycarbonyl, and heteroarylcarbonyloxy each of which is, optionally, substituted with C<sub>1-10</sub> alkyl, CN, COOH, NO<sub>2</sub>, NH<sub>2</sub>, SO<sub>2-4</sub>, C<sub>1-20</sub> heteroalkyl, C<sub>2-20</sub> alkenyl, alkynyl, alkynyl-aryl, alkynyl-heteroaryl, aryl, C<sub>1-20</sub> alkyl-aryl, C<sub>2-20</sub> alkenyl-aryl, heteroaryl, C<sub>1-20</sub> alkyl-heteroaryl, C<sub>2-20</sub> alkenyl-heteroaryl, cycloalkyl, heterocycloalkyl, C<sub>1-20</sub> alkyl-heterocycloalkyl, and C<sub>1-20</sub> alkyl-cycloalkyl, any of which may be, optionally, substituted with a moiety selected from the group consisting of C<sub>1-6</sub> alkyl, halogen, OH, NH<sub>2</sub>, CN, NO<sub>2</sub>, COOH, or SO<sub>2-4</sub>. In other embodiments, the substituted carboxylic group can be substituted with a moiety selected from the group consisting of C<sub>1-10</sub> alkyl, CN, COOH, NO<sub>2</sub>, NH<sub>2</sub>, SO<sub>2-4</sub>, C<sub>1-20</sub> heteroalkyl, C<sub>2-20</sub> alkenyl, alkynyl, alkynyl-aryl, alkynyl-heteroaryl, aryl, C<sub>1-20</sub> alkyl-aryl, C<sub>2-20</sub> alkenyl-aryl, heteroaryl, C<sub>1-20</sub> alkyl-heteroaryl, C<sub>2-20</sub> alkenyl-heteroaryl, cycloalkyl, heterocycloalkyl, C<sub>1-20</sub> alkyl-heterocycloalkyl, and C<sub>1-20</sub> alkyl-cycloalkyl, any of which may be, optionally, substituted with a moiety selected from the group consisting of C<sub>1-6</sub> alkyl, halogen, OH, NH<sub>2</sub>, CN, NO<sub>2</sub>, COOH, or SO<sub>2-4</sub>. Exemplary heterocyclic groups include, but are not limited to, morpholine, triazole, imidazole, pyrrolidine, piperidine, piperazine, pyrrole, dihydropyridine, aziridine, thiazolidine, thiazoline, thiadiazolidine, and thiadiazoline.

In specific embodiments, X can be hydroxyl, hydroxycarbonyl, 1-methyl-1-cyclohexylcarbonyloxy, 1-methyl-1-cyclohexylmethoxycarbonyl, 5-ethyl-2-pyridyl-acetoxy, 5-ethyl-2-pyridylmethoxy-carbonyl, (R)-6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxy, (S)-6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxy, (R)-6-hydroxy-2,5,7,8-tetra-methylchroman-2-ylmethoxy -carbonyl, (S)-6-hydroxy-2,5,7,8-tetramethylchroman-2-ylmethoxycarbonyl, (R)-5-hydroxy-2,2,4,6,7-pentamethyl-2,3-

dihydrobenzofuran-3-carboxy, (S)-5-hydroxy-2,2,4,6,7-pentamethyl-2,3-dihydrobenzofuran-3-carboxy, (R)-5-hydroxy-2,2,4,6,7-penta-methyl-2,3-dihydrobenzofuran-3-methoxycarbonyl, (S)-5-hydroxy-2,2,4,6,7-pentamethyl -2,3-dihydrobenzofuran-3-methoxycarbonyl, 2-hydroxybenzoyloxy, or 2,4-dihydroxybenzoyloxy.

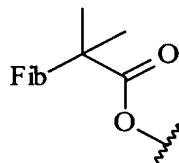
5 In other embodiments, X can be



wherein Hetero is an aromatic, cyclic, or alicyclic moiety that can contain heteroatoms. In certain specific embodiments, Hetero is an aromatic, cyclic, or alicyclic moiety that contains heteroatoms that are generally part of the structure of the statin-family of lipid lowering agents. Preferred examples include, but are not limited to, 2-(4-fluorophenyl)-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1-(1H-pyrrol)yl, a component of atorvastatin, and 1,2,3,7,8,8a-hexahydro-1-(2-methylbutanoyl)oxy-3,7-dimethyl-8-naphthalenyl, a component of lovastatin.

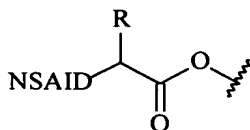
Alternatively, X can be

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wherein Fib is an aromatic, cyclic, or alicyclic moiety that can contain heteroatoms. In certain specific embodiments, Fib moieties are part of the fibrate-family of lipid lowering agents. Preferred examples include, but are not limited to 4-(4-chlorobenzoyl)phenoxy, a component of fenofibric acid, 4-chlorophenoxy, a component of clofibric acid, and 3-(2,5-xylyloxy)-1-propyl, a component of gemfibrozil.

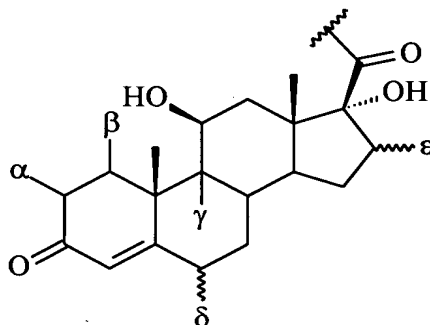
25 Alternatively, X can be



wherein R is hydrogen or methyl, and in which NSAID means an aromatic, alkyl, or cycloalkyl moiety that may contain heteroatoms and that are generally part of the

family of non-steroidal anti-inflammatory agents. Preferred examples include, but are not limited to 4-(2-methyl-1-propyl)phenyl, 2-(2,6-dichloro-1-phenyl)aminophenyl, 6'-methoxy-2'-naphthyl, and 6'-methoxy-2'-naphthylmethyl.

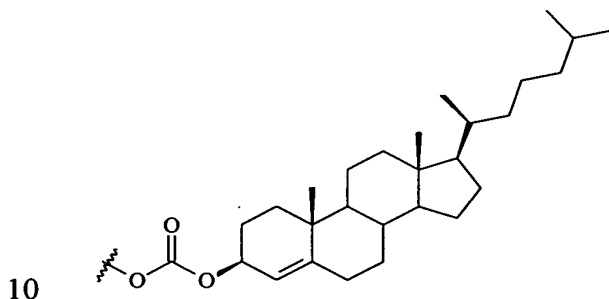
In another embodiment, X can be



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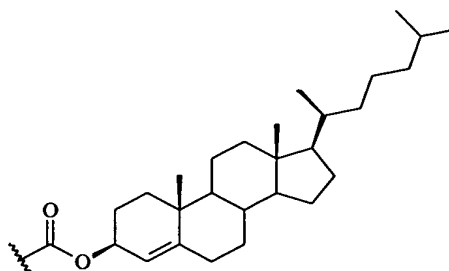
where  $\alpha$  and  $\beta$  are hydrogen or  $\alpha$  and  $\beta$  form a bond, and where  $\gamma$ ,  $\delta$ , and  $\epsilon$ , are independently hydrogen, hydroxy, fluoro, chloro, or methyl.

Alternatively, X can be



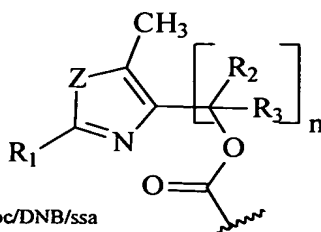
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or



X can also be of the general formula

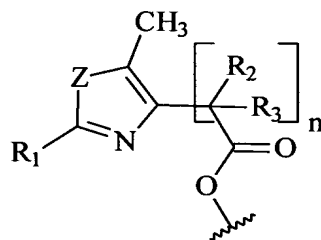
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In such embodiments, n is 0 or 1, R<sub>2</sub> and R<sub>3</sub> are independently hydrogen or methyl; Z is N, O, or S; and R<sub>1</sub> is aryl or heteroaryl, alkyl or heteroalkyl. Preferred non-limiting  
 5 examples include compounds where R<sub>1</sub> is phenyl, 4-fluorophenyl, 4-methoxyphenyl, 3-methyl-2-thiophenyl, 5-methyl-2-thiophenyl, 5-methyl-3-isoxazolyl, 2-pyridyl, 4-pyridyl, 2-pyrazinyl, 2-hydroxybenzoyl, or 2,4-dihydroxybenzoyl.

Other embodiments provide compounds wherein X is

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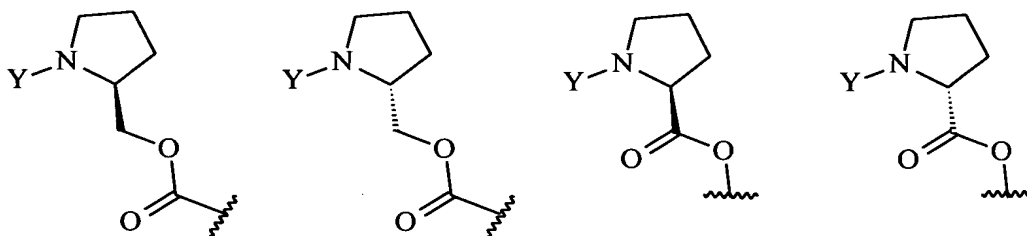
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in which n is 0 or 1, R<sub>2</sub> and R<sub>3</sub> are independently hydrogen or methyl; Z is N, O, or S; and R<sub>1</sub> is aryl or heteroaryl, alkyl or heteroalkyl. Preferred non-limiting examples  
 include compounds where R<sub>1</sub> is phenyl, 4-fluorophenyl, 4-methoxyphenyl, 3-methyl-2-thiophenyl, 5-methyl-2-thiophenyl, 5-methyl-3-isoxazolyl, 2-pyridyl, 4-pyridyl, 2-pyrazinyl, 2-hydroxybenzoyl, or 2,4-dihydroxybenzoyl.

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In other embodiments, X is a 1-substituted (R)-pyrrolidine-2-methoxycarbonyl, (S)-pyrrolidine-2-methoxycarbonyl, (R)-pyrrolidine-2-carboxy, or (S)-pyrrolidine-2-carboxy, having the following formulas

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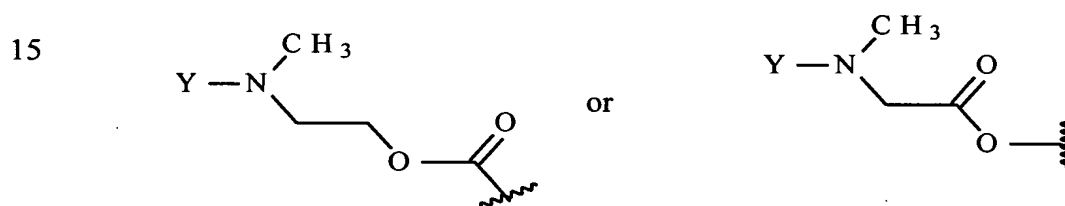


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in which Y is aryl or heteroaryl, alkyl or heteroalkyl. Preferred non-limiting  
 examples include compounds where Y is (R)-6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxy, (S)-6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxy, (R)-6-hydroxy-2,5,7,8-tetramethylchroman-2-ylmethoxycarbonyl, (S)-6-hydroxy-2,5,7,8-tetramethylchroman-2-ylmethoxycarbonyl, (R)-5-hydroxy-2,2,4,6,7-pentamethyl-2,3-

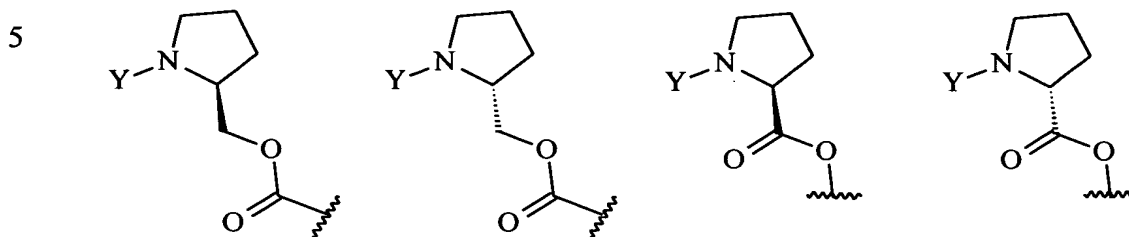
dihydrobenzofuran-3-carboxy, (S)-5-hydroxy-2,2,4,6,7-pentamethyl-2,3-dihydrobenzofuran-3-carboxy, (R)-5-hydroxy-2,2,4,6,7-pentamethyl-2,3-dihydrobenzofuran-3-methoxycarbonyl, (S)-5-hydroxy-2,2,4,6,7-pentamethyl-2,3-dihydrobenzofuran-3-methoxycarbonyl, 5-chloro-2-pyridyl, 5-methyl-2-pyridyl, 3-chloro-2-pyridyl, 4-methyl-2-pyridyl, 2-pyridyl, 2-benzoxazolyl, 2-benzothiazolyl, 5-amino-2-pyridyl, 5-nitro-2-pyridyl, 2-pyrazinyl, 4-phenyl-2-oxazoliny, 5-methyl-2-thiazoliny, 4,5-dimethyl-2-oxazoliny, 4,5-dimethyl-2-thiazoliny, 5-phenyl-2-thiazoliny, 2-thiazoliny, 4-methyl-5-phenyl-2-thiazoliny, 5-methyl-4-phenyl-2-thiazoliny, 2-piperidinyl, 4-phenyl-2-piperidinyl, 6-methyl-2-pyridiny, 6-methoxy-2-pyridiny, 2-hydroxybenzoyl, or 2,4-dihydroxybenzoyl.

Alternatively X is an N-substituted 2-methylaminoethoxycarbonyl or a N-substituted 2-methylaminoacetoxyl, having the following formulas:

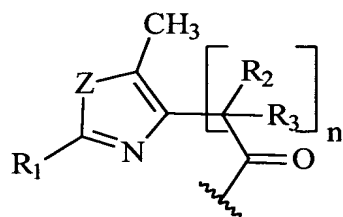


in which Y is aryl or heteroaryl, alkyl or heteroalkyl. Preferred non-limiting examples include compounds where Y is (R)-6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxy, (S)-6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxy, (R)-6-hydroxy-2,5,7,8-tetramethylchroman-2-ylmeth-oxycarbonyl, (S)-6-hydroxy-2,5,7,8-tetramethylchroman-2-ylmethoxycarbonyl, (R)-5-hydroxy-2,2,4,6,7-pentamethyl-2,3-dihydrobenzofuran-3-carboxy, (S)-5-hydroxy-2,2,4,6,7-pentamethyl-2,3-dihydrobenzofuran-3-carboxy, (R)-5-hydroxy-2,2,4,6,7-pentamethyl-2,3-dihydrobenzofuran-3-methoxycarbonyl, (S)-5-hydroxy-2,2,4,6,7-pentamethyl-2,3-dihydrobenzofuran-3-methoxycarbonyl, 5-chloro-2-pyridyl, 5-methyl-2-pyridyl, 3-chloro-2-pyridyl, 4-methyl-2-pyridyl, 2-pyridyl, 2-benzoxazolyl, 2-benzothiazolyl, 5-amino-2-pyridyl, 5-nitro-2-pyridyl, 2-pyrazinyl, 4-phenyl-2-oxazoliny, 5-methyl-2-thiazoliny, 4,5-dimethyl-2-oxazoliny, 4,5-dimethyl-2-thiazoliny, 5-phenyl-2-thiazoliny, 2-thiazoliny, 4-methyl-5-phenyl-2-thiazoliny, 5-methyl-4-phenyl-2-thiazoliny, 2-piperidinyl, 4-phenyl-2-piperidinyl, 6-methyl-2-pyridiny, 6-methoxy-2-pyridiny, 2-hydroxybenzoyl, or 2,4-dihydroxybenzoyl.

X can also be a 1-substituted (R)-pyrrolidine-2-methoxycarbonyl, (S)-pyrrolidine-2-methoxycarbonyl, (R)-pyrrolidine-2-carboxy, or (S)-pyrrolidine-2-carboxy, having the following formulas:

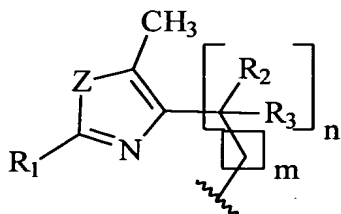


wherein Y is



15 n is 0 or 1; R<sub>2</sub> and R<sub>3</sub> are independently hydrogen or methyl; Z is N, O, or S; and R<sub>1</sub> is aryl or heteroaryl, alkyl or heteroalkyl. Preferred non-limiting examples include compounds where R<sub>1</sub> is phenyl, 4-fluorophenyl, 4-methoxyphenyl, 3-methyl-2-thiophenyl, 5-methyl-2-thiophenyl, 5-methyl-3-isoxazolyl, 2-pyridyl, 4-pyridyl, or 2-pyrazinyl; or

20 Y is

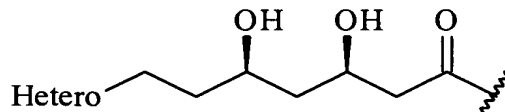


n is 0 or 1; m is 0 or 1; R<sub>2</sub> and R<sub>3</sub> are independently hydrogen or methyl; Z is N, O, or S; and R<sub>1</sub> is aryl or heteroaryl, alkyl or heteroalkyl. Preferred non-limiting examples include compounds where R<sub>1</sub> is phenyl, 4-fluorophenyl, 4-methoxyphenyl, 3-methyl-



2-thiophenyl, 5-methyl-2-thiophenyl, 5-methyl-3-isoxazolyl, 2-pyridyl, 4-pyridyl, or 2-pyrazinyl; or

Y is

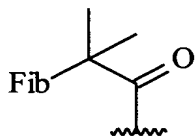


5

wherein Hetero is an aromatic, cyclic, or alicyclic moiety that usually contains heteroatoms. In certain specific embodiments, these moieties are part of the structure of the statin-family of lipid lowering agents. Preferred examples include, but are not limited to, 2-(4-fluorophenyl)-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1-(1H-pyrrol)yl, a component of atorvastatin, and 1,2,3,7,8,8a-hexahydro-1-(2-methylbutanoyl)oxy-3,7-dimethyl-8-naphthalenyl, a component of lovastatin; or

10

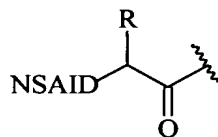
Y is



15 wherein Fib is an aromatic, cyclic, or alicyclic moiety that contains heteroatoms. In some embodiments, these moieties are part of the fibrate-family of lipid lowering agents. Preferred examples include, but are not limited to 4-(4-chlorobenzoyl)phenoxy, a component of fenofibric acid, 4-chlorophenoxy, a component of clofibric acid, and 3-(2,5-xilyloxy)-1-propyl, a component of gemfibrozil; or

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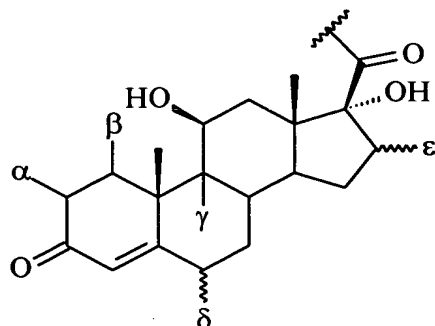
Y is



wherein R is hydrogen or methyl, and in which NSAID means an aromatic, alkyl, or cycloalkyl moiety that may contain heteroatoms and that are generally part of the family of non-steroidal anti-inflammatory agents. Preferred examples include, but are not limited to 4-(2-methyl-1-propyl)phenyl, 2-(2,6-dichloro-1-phenyl)aminophenyl, 6'-methoxy-2'-naphthyl, and 6'-methoxy-2'-naphthylmethyl or

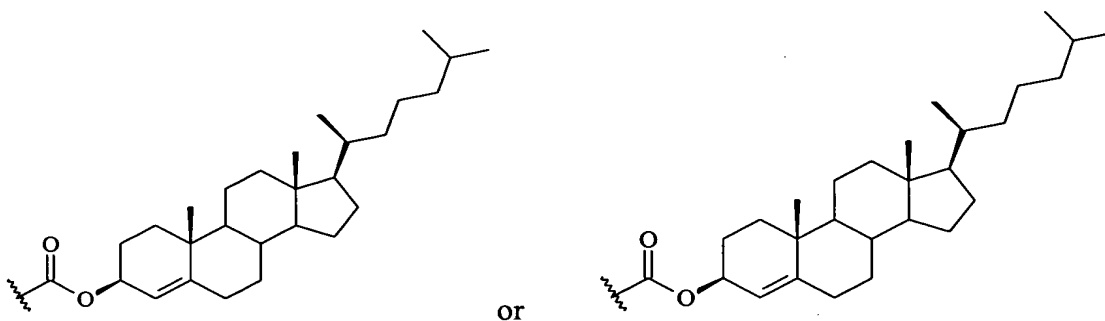
25

Y can be

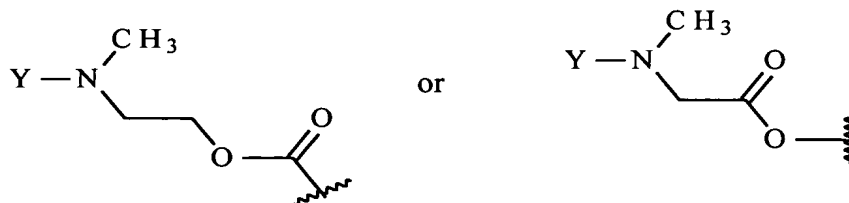


where  $\alpha$  and  $\beta$  are hydrogen or  $\alpha$  and  $\beta$  form a bond, and where  $\gamma$ ,  $\delta$ , and  $\epsilon$ , are independently hydrogen, hydroxy, fluoro, chloro, or methyl; or

5 Y can be

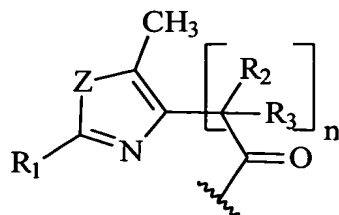


Alternatively X can be an N-substituted 2-methylaminoethoxycarbonyl or an  
10 N-substituted 2-methylaminoacetoxy, having the following formulas:



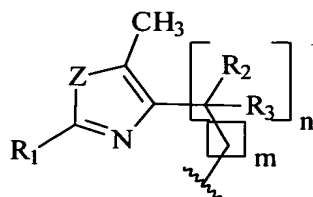
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wherein Y is



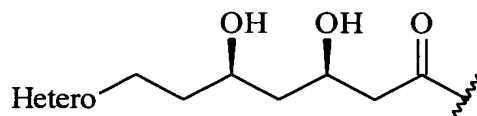
- 5 n is 0 or 1; R<sub>2</sub> and R<sub>3</sub> are independently hydrogen or methyl; Z is N, O, or S; and R<sub>1</sub> is aryl, heteroaryl, alkyl or heteroalkyl. Preferred non-limiting examples include compounds where R<sub>1</sub> is phenyl, 4-fluorophenyl, 4-methoxyphenyl, 3-methyl-2-thiophenyl, 5-methyl-2-thiophenyl, 5-methyl-3-isoxazolyl, 2-pyridyl, 4-pyridyl, or 2-pyrazinyl, 2-hydroxybenzoyl, or 2,4-dihydroxybenzoyl; or

10 Y is



- n is 0 or 1; m is 0 or 1; R<sub>2</sub> and R<sub>3</sub> are independently hydrogen or methyl; Z is N, O, or S; and R<sub>1</sub> is aryl or heteroaryl, alkyl or heteroalkyl. Preferred non-limiting examples include compounds where R<sub>1</sub> is phenyl, 4-fluorophenyl, 4-methoxyphenyl, 3-methyl-2-thiophenyl, 5-methyl-2-thiophenyl, 5-methyl-3-isoxazolyl, 2-pyridyl, 4-pyridyl, 2-pyrazinyl, 2-hydroxybenzoyl, or 2,4-dihydroxybenzoyl; or

Y is

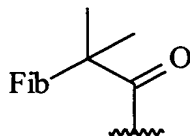


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wherein Hetero is an aromatic, cyclic, or alicyclic moiety that contains heteroatoms. In certain specific embodiments, these moieties are part of the structure of the statin-family of lipid lowering agents. Preferred examples include, but are not limited to, 2-(4-fluorophenyl)-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1-(1H-

pyrrol)yl, a component of atorvastatin, and 1,2,3,7,8,8a-hexahydro-1-(2-methylbutanoyl)oxy-3,7-dimethyl-8-naphthalenyl, a component of lovastatin; or

Y is

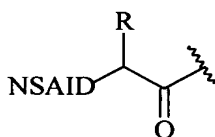


5

wherein Fib is an aromatic, cyclic, or alicyclic moiety that contains heteroatoms. In some embodiments, these moieties are part of the fibrate-family of lipid lowering agents. Preferred examples include, but are not limited to 4-(4-chlorobenzoyl)phenoxy, a component of fenofibric acid, 4-chlorophenoxy, a component of clofibric acid, and 3-(2,5-xylyloxy)-1-propyl, a component of gemfibrozil; or

10

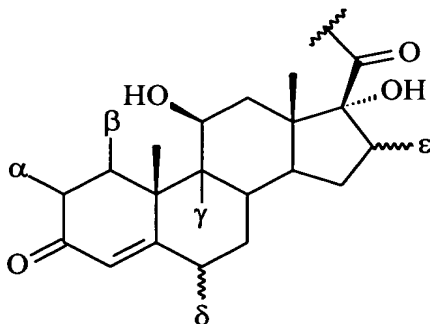
Y is



wherein R is hydrogen or methyl, and in which NSAID means an aromatic, alkyl, or cycloalkyl moiety that may contain heteroatoms and that are generally part of the family of non-steroidal anti-inflammatory agents. Preferred examples include, but are not limited to 4-(2-methyl-1-propyl)phenyl, 2-(2,6-dichloro-1-phenyl)aminophenyl, 6'-methoxy-2'-naphthyl, and 6'-methoxy-2'-naphthylmethyl; or

15

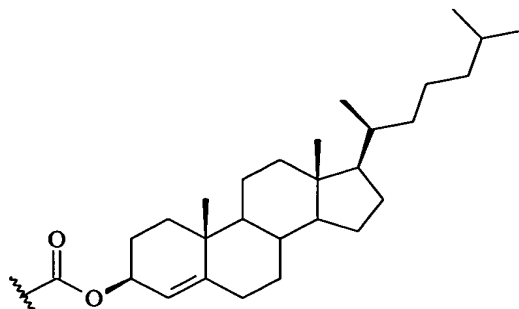
Y can be



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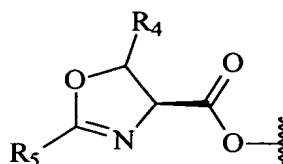
where  $\alpha$  and  $\beta$  are hydrogen or  $\alpha$  and  $\beta$  form a bond, and where  $\gamma$ ,  $\delta$ , and  $\epsilon$ , are independently hydrogen, hydroxy, fluoro, chloro, or methyl; or

Y can be



Other embodiments provide compounds wherein X is

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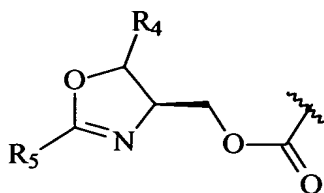


R<sub>4</sub> is hydrogen or methyl, and where R<sub>5</sub> is aryl or heteroaryl, alkyl or heteroalkyl.

10 Preferred non-limiting examples include compounds where R<sub>5</sub> is phenyl, 4-fluorophenyl, 4-methoxyphenyl, 3-methyl-2-thiophenyl, 5-methyl-2-thiophenyl, 5-methyl-3-isoxazolyl, 2-pyridyl, 4-pyridyl, 2-pyrazinyl, (R)-6-hydroxy-2,5,7,8-tetramethyl-2-chromanyl, (S)-6-hydroxy-2,5,7,8-tetramethyl-2-chromanyl, (R)-5-hydroxy-2,2,4,6,7-pentamethyl-2,3-dihydro-3-benzofuranyl, or (S)-5-hydroxy-2,2,4,6,7-pentamethyl-2,3-dihydro-3-benzofuranyl.

15

X can also be



20

wherein R<sub>4</sub> is hydrogen or methyl, and where R<sub>5</sub> is aryl or heteroaryl, alkyl or heteroalkyl. Preferred non-limiting examples include compounds where R<sub>5</sub> is phenyl, 4-fluorophenyl, 4-methoxyphenyl, 3-methyl-2-thiophenyl, 5-methyl-2-thiophenyl, 5-methyl-3-isoxazolyl, 2-pyridyl, 4-pyridyl, 2-pyrazinyl, (R)-6-hydroxy-2,5,7,8-tetramethyl-2-chromanyl, (S)-6-hydroxy-2,5,7,8-tetramethyl-2-chromanyl, (R)-5-hydroxy-2,2,4,6,7-pentamethyl-2,3-dihydro-3-benzofuranyl, or (S)-5-hydroxy-2,2,4,6,7-pentamethyl-2,3-dihydro-3-benzofuranyl.

25

In one embodiment, A is NH; B is sulfur (S); P and Q are a double bond or hydrogen (H); E is hydrogen (H) and is attached to each of D<sub>1</sub> through D<sub>6</sub>; D<sub>1</sub> through D<sub>6</sub> are carbon (C); and X can be any of the structures provided *supra*.

5 Modifications of the compounds disclosed herein can readily be made by those skilled in the art. Thus, analogs, derivatives, and salts of the exemplified compounds are within the scope of the subject invention. With a knowledge of the compounds of the subject invention, and their structures, skilled chemists can use known procedures to synthesize these compounds from available substrates.

10 As used in this application, the terms "analogs" and "derivatives" refer to compounds which are substantially the same as another compound but which may have been modified by, for example, adding additional side groups. The terms "analogs" and "derivatives" as used in this application also may refer to compounds which are substantially the same as another compound but which have atomic or molecular substitutions at certain locations in the compound.

15 Analogs or derivatives of the exemplified compounds can be readily prepared using commonly known, standard reactions. These standard reactions include, but are not limited to, hydrogenation, methylation, acetylation, and acidification reactions. For example, new salts within the scope of the invention can be made by adding mineral acids, e.g., HCl, H<sub>2</sub>SO<sub>4</sub>, etc., or strong organic acids, e.g., formic, oxalic, etc.,  
20 in appropriate amounts to form the acid addition salt of the parent compound or its derivative. Also, synthesis type reactions may be used pursuant to known procedures to add or modify various groups in the exemplified compounds to produce other compounds within the scope of the invention.

25 The subject invention further provides methods of treating disorders, such as diabetes, atherosclerosis, hypercholesterolemia, and hyperlipidemia, comprising the administration of a therapeutically effective amount of esterified thiazolidinedione analogs to an individual in need of treatment. Thiazolidinedione based compounds include troglitazone (for example, REZULIN), pioglitazone, and rosiglitazone. Accordingly, the subject invention provides esterified thiazolidinedione analogs and  
30 pharmaceutical compositions of these esterified compounds. The compounds and compositions according to the invention can also be administered in conjunction with other therapeutic compounds, therapeutic regimens, compositions, and agents suitable for the treatment of disorders, such as diabetes, atherosclerosis, hypercholesterolemia,

and hyperlipidemia. Thus, the invention includes combination therapies wherein the compounds and compositions of the invention are used in conjunction with other therapeutic agents for the treatment of disorders, such as diabetes, atherosclerosis, hypercholesterolemia, and hyperlipidemia.

5           The compounds of this invention have therapeutic properties similar to those of the unmodified parent compounds. Accordingly, dosage rates and routes of administration of the disclosed compounds are similar to those already used in the art and known to the skilled artisan (see, for example, *Physicians' Desk Reference*, 54<sup>th</sup> Ed., Medical Economics Company, Montvale, NJ, 2000).

10           The compounds of the subject invention can be formulated according to known methods for preparing pharmaceutically useful compositions. Formulations are described in detail in a number of sources that are well known and readily available to those skilled in the art. For example, *Remington's Pharmaceutical Science* by E.W. Martin describes formulations that can be used in connection with  
15 the subject invention. In general, the compositions of the subject invention are formulated such that an effective amount of the bioactive compound(s) is combined with a suitable carrier in order to facilitate effective administration of the composition.

          In accordance with the subject invention, pharmaceutical compositions are  
20 provided which comprise, as an active ingredient, an effective amount of one or more of the compounds of the invention and one or more non-toxic, pharmaceutically acceptable carriers or diluents. Examples of such carriers for use in the invention include ethanol, dimethyl sulfoxide, glycerol, silica, alumina, starch, and equivalent carriers and diluents. Additional therapeutic agents suitable for the treatment of  
25 disorders such as diabetes, atherosclerosis, hypercholesterolemia, and hyper-lipidemia can also be incorporated into pharmaceutical agents according to the invention.

          Further, acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, pills, capsules, cachets, suppositories and dispersible granules. A solid carrier can be one or more substances that may act as  
30 diluents, flavoring agents, solubilizers, lubricants, suspending agents, binders, preservatives, tablet disintegrating agents or encapsulating materials.

          The disclosed pharmaceutical compositions may be subdivided into unit doses containing appropriate quantities of the active component. The unit dosage form can

be a packaged preparation, such as packeted tablets, capsules, and powders in paper or plastic containers or in vials or ampoules. Also, the unit dosage can be a liquid based preparation or formulated to be incorporated into solid food products, chewing gum, or lozenge.

5           Compounds **1** through **4** (of Table I) can be conveniently prepared by the Knoevenagel reaction between an aldehyde and thiazolidine-2,4-dione, using for example sodium acetate in acetic anhydride, or piperidine and benzoic acid in methylene chloride as a reaction medium. This is illustrated in Figure 2 and Figure 3. Alternatively, compound **1** can be prepared by the method described in Figure 4. In  
10 this reaction scheme, *para*-anisidine undergoes a diazotation reaction with sodium nitrite and hydrochloric acid. The diazonium chloride salt undergoing, in turn, a radicalar reaction with methyl acrylate and then a cyclization reaction with thiourea, the product of which is hydrolyzed to the thiazolidinedione molecule.

          The compounds described in Table I (compounds **5** to **32**) can all be made via  
15 an esterification reaction between **1** or **2** and an appropriately substituted carboxylic acid, or between **3** or **4** and an appropriately substituted alcohol. The esterification reaction can be facilitated by the presence of a catalyst in the reaction medium, such as a small amount of concentrated sulfuric acid for example. Preferably, especially if the alpha-position to the carbonyl is an asymmetric center, an activated functional  
20 derivative of the carboxylic acid is made. Numerous functional derivatives of carboxylic acids used in esterification reactions have been described in the scientific literature. The most commonly used activated functional derivatives are acyl chlorides, anhydrides and mixed anhydrides, and activated esters. In one aspect of this invention dicyclohexyl carbodiimide (DCC) was used as an activating agent  
25 (Figure 5).

          Compounds **33** to **104** are functionalized 5-methyloxazole and functionalized 5-methylthiazole derivatives. They all have various functional groups attached to the 2-position ( $R_1$  in Tables II to V), and at the 4-position, which is the enzymatically labile link with the thiazolidine portion of the molecule. The enzymatically labile link  
30 is either an ester ( $\text{COO-}$ ) or a reverse ester ( $\text{OOC-}$ ) and can be substituted with 0, 1, or 2 methyl groups at the alpha-position from the oxazole or thiazole ring ( $R_2$  and  $R_3$  in Tables II to V).



The synthesis of compounds **33** to **104** is described in general terms in Figures 7-10. Figure 6 describes the synthesis of the 4-oxazoleacetic acid and the 4-oxazoleethanol moiety starting from aspartic acid derivatives in which R<sub>2</sub> and R<sub>3</sub> are methyl or hydrogen. In a typical example,  $\gamma$ -benzyl aspartate is acetylated and then  
5 decarboxylated to benzyl 3-acetamido-4-oxovalerate using acetic anhydride as an acetylating agent followed by potassium hydroxide in order to obtain the decarboxylated product. This in turn is transformed into methyl 3-amino-4-oxovalerate using standard hydrolytic and esterification procedures, for example refluxing in dilute hydrochloric acid followed by reaction in thionyl chloride and  
10 methanol. The R<sub>1</sub> group is then introduced by acylating the 3-amino group using the appropriate acyl or aroyl chloride. There is almost no limitation to the nature of the R<sub>1</sub> group being introduced at this stage, as shown in Tables II to V where various R<sub>1</sub> groups are described. Cyclization to an oxazole ring is then effected using sulfuric acid as a catalyst in ethyl acetate as a solvent. At this stage, ester hydrolysis using  
15 lithium hydroxide in methanol gives the desired 4-oxazoleacetic acid derivatives, whereas reduction of the ester with lithium aluminum hydride or reduction of the acid using diborane gives the 4-oxazoleethanol analogs.

Figure 7 describes the synthesis of the 4-oxazolecarboxylic acid and 4-oxazolemethanol groups. The synthesis starts from ethyl acetoacetate in which a 2-  
20 amino-group is introduced via oxime formation followed by reduction with zinc powder. The synthesis then proceeds as before, where the R<sub>1</sub> group is introduced by acylating the amino group, followed by cyclization with sulfuric acid in ethyl acetate, and finally ester cleavage or reduction to the alcohol.

Figure 8 shows how steric hindrance can be introduced under the form of  
25 methyl groups on the 4-methanol moiety. Starting from pentane-2,4-dione, following the same synthetic sequence as in Figure 7 leads to the 4-acetyloxazole compounds which can be reduced by sodium borohydride to the 4-(1-ethyl)oxazole. Alternatively, the compounds can be transformed by methylmagnesium iodide into the tertiary alcohol analogs. In another embodiment, condensation of a thioamide  
30 with methyl 4-bromo-3-oxopentanoate gives methyl 4-thiazoleacetate, as described in Figure 9. Ester cleavage with lithium hydroxide or reduction with lithium aluminum hydride gives the corresponding acid or the alcohol, respectively.

Compounds **105** to **224** in Tables VI to XVII all have an amino acid or an amino alcohol as part of their structure. Their synthesis is described in Figures 10 to 18. Any amino acid can be used in the synthesis of compounds according to this aspect of the invention. In certain embodiments, the amino acid group can be either  
5 proline or N-methyl glycine and the amino alcohol group is their alcohol equivalent, *i.e.*, prolinol or N-methyl glycinol, respectively. As shown in Figures 10 to 13, the reaction of an alkyl chloride or a 2-heteroaryl chloride with proline, prolinol, N-methyl glycine, or N-methyl glycinol, in THF and triethylamine gives the corresponding N-alkyl or N-heteroaryl adduct, respectively. When these adducts are  
10 carboxylic acids, such as in Figures 10 and 12, they react with 5-(4-hydroxybenzyl)thiazolidine-2,4-dione in the presence of DCC and DMAP to give compounds **105-108, 111, 112, 125-128, 131, 132, 185-188, 191, 192**. Carboxylic acid adducts react with 5-(4-hydroxybenzylidene)thiazolidine-2,4-dione in the presence of DCC and DMAP to give compounds **115-118, 121, 122, 135-138, 141,**  
15 **142, 195-198, 201, 202**. When these adducts are alcohols, such as in Figures 11 and 13, they react with 5-(4-carboxybenzyl)thiazolidine-2,4-dione in the presence of DCC and DMAP to give compounds **145-148, 151, 152, 165-168, 171, 172, 205-208, 211, 212**. Alcohol adducts react with 5-(4-carboxybenzylidene)thiazolidine-2,4-dione in the presence of DCC and DMAP to give compounds **155-158, 161, 162, 175-178,**  
20 **181, 182, 215-218, 221, 222**.

Alternatively, the amino acid or amino alcohol group can be linked to another group via an amide function, such as described in Figures 14 to 17. The synthesis of such compounds is straightforward. When the compounds contain an amino acid, as in Figures 14 and 16, the synthetic sequence is an amide bond formation, ester  
25 deprotection, and ester formation.

As an illustrative example, (R)-Trolox<sup>®</sup> is combined with L-proline methyl ester, in the presence of DCC and DMAP in methylene chloride to form an amide intermediate. The methyl ester of the proline group is then cleaved with lithium hydroxide in methanol, and the resulting carboxylic acid is combined with 5-(4-  
30 hydroxybenzyl)thiazolidine-2,4-dione in DCC/DMAP/methylene chloride to give compound **109**. The (S)-isomer, compound **110**, is made in a similar way. The same kind of synthetic scheme leads to compounds **113, 114, 119, 120, 123, 124, 129, 130, 133, 134, 139, 140, 143, 144, 189, 190, 193, 194, 199, 200, 203, and 204**.

When the compounds contain an amino alcohol, as in Figures 15 and 17, the synthetic sequence is an amide bond formation, followed by an ester bond formation. As an illustrative example, (R)-Trolox<sup>®</sup> is combined with L-prolinol in the presence of DCC and DMAP in methylene chloride to form an amide intermediate. The resulting amide is combined with 5-(4-carboxybenzyl)thiazolidine-2,4-dione in DCC/DMAP/methylene chloride to give compound 149. The (S)-isomer, compound 150, is made in a similar way. The same kind of synthetic scheme leads to compounds 153, 154, 159, 160, 163, 164, 169, 170, 173, 174, 179, 180, 183, 184, 209, 210, 213, 214, 219, 220, 223, and 224.

Compounds 225 to 242 (Table XVIII) are oxazoline-4-carboxylic acid types of compounds. Their synthesis (Figure 18) starts from serine ( $R_5=H$ ) or from threonine ( $R_5=CH_3$ ) benzyl ester. The ester is coupled with an alkyl or an arylcarboxylic acid using for example EDC as a coupling agent. The serine or threonine group then cyclizes into an oxazoline upon treatment with thionyl chloride. Coupling with 5-(4-hydroxybenzyl)thiazolidine-2,4-dione using DCC/DMAP/methylene chloride gives compounds 225 to 242.

Compounds 243 to 248 (Table XIX) are thiazolidinedione molecules where X is a group containing a substituted 2-methyl-2-propionyl residue. Examples include the 2-methyl-2-(4-chlorophenoxy)propionyl moiety (clofibryl moiety), the 2-methyl-2-[4-(4-chlorobenzoyl)phenoxy]propionyl moiety (fenofibryl moiety), and 2,2-dimethyl-5-(2,5-xylyloxy)valeryl moiety (gemfibrozil moiety).

Compounds 249 to 252 (Table XX) are thiazolidinedione molecules where X is a group containing a substituted (R,R)-3,5-dihydroxyheptanoyl residue. Examples include the ( $\beta R$ ,  $\delta R$ )-2-(4-fluorophenyl)-5-(1-methylethyl)-3-phenyl-4-[(phenyl-amino)carbonyl] 1H-pyrrole-1-( $\beta, \delta$ , dihydroxy)heptanoyl group (atorvastatin), and the 1,2,3,7,8,8a-hexahydro-1-(2-methylbutanoyl)oxy-3,7-dimethylnaphthalenyl-8-[(3R,5R)-7-heptan]oyl group (lovastatin). The synthesis of these compounds proceeds as in the examples of Table I, (*i.e.*, by a simple esterification procedure between the lipid-lowering agent and compound 1 or compound 2).

Compounds 253 to 260 (Table XXI) are thiazolidinedione molecules where X is a group containing an arylacetic acid residue, such as in molecules that have non-steroidal anti-inflammatory properties. In these examples, the X group is an

ibuprofen, ibufenac, naproxen, diclofenac, or nabumetone residue. The synthesis of these compounds is a simple ester formation reaction between the X group and compound 1 (P and Q are hydrogen) or compound 2 (P and Q form a bond).

Compounds 261 to 268 (Table XXII) are thiazolidinedione molecules where X is a group containing a cortienic acid residue, such as in molecules that have glucocorticoid anti-inflammatory properties. In these examples, the X group is a cortienic acid, 1,2-dihydrocortienic acid, 6 $\alpha$ , 9 $\alpha$ -difluoro-1,2-dihydrocortienic acid, and a 9 $\alpha$ -fluoro-16 $\alpha$ -methyl-1,2-dihydrocortienic acid residue. The synthesis of these compounds is a simple ester formation reaction between the X group and compound 1 (P and Q are hydrogen) or compound 2 (P and Q form a bond). Cortienic acid, one of the many metabolites of hydrocortisone in man, can be synthesized from hydrocortisone by oxidation with sodium periodate. The substituted cortienic acid analogs can be made in an identical manner from the corresponding substituted glucocorticoids. This oxidation procedure is described in detail in [Druzgala P.: Novel Soft Anti-inflammatory Glucocorticoids for Topical Application. Ph.D. Dissertation (1985), University of Florida, Gainesville, FL, hereby incorporated by reference in its entirety].

Representative compounds were chosen and evaluated for activity on serum glucose and insulin levels in non-insulin dependent diabetic mellitus (NIDDM) KK-A<sup>y</sup> male mice. Post-treatment data for each group were transferred to a percentage of pretreatment values and unpaired Student's t test was used for comparison between vehicle and test substance treated groups. Results show a significant reduction of both serum glucose and serum insulin relative to the vehicle control group. Reduction in serum glucose and serum insulin levels were comparable to the reduction observed in the troglitazone-treated animals. The results are presented in Table XXI and in Figures 19 and 20.

## EXAMPLES

Example 1- To (S)-2-pyrrolidinemethanol (3.96g) in THF (30ml) is added 2-chlorobenzoxazole (5.90g) also in THF (80ml) and then, dropwise, triethylamine (3.96g). Stir at 50°C for 4 hours. Cool to room temperature and filter out the solid.

Evaporate the solvent and dissolve the crude product in 5ml of methylene chloride. Pass through a silica plug (50g) in a fritted filter funnel, and elute with methanol/methylene chloride (10:90), applying suction until the product has been collected. The yield of (S)-1-(2-benzoxazolyl)-2-hydroxymethylpyrrolidine is 8.2g.

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Example 2-To (S)-2-pyrrolidinemethanol (3.96g) in THF (30ml) is added 2-chlorobenzothiazole (6.50g) also in THF (80ml) and then, dropwise, triethylamine (3.96g). Stir at 50°C for 4 hours. Cool to room temperature and filter out the solid. Evaporate the solvent and dissolve the crude product in 5ml of methylene chloride. Pass through a silica plug (50g) in a fritted filter funnel, and elute with methanol/methylene chloride (10:90), applying suction until the product has been collected. The yield of (S)-1-(2-benzothiazolyl)-2-hydroxymethylpyrrolidine is 8.8g.

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Example 3- To (R)-2-pyrrolidinemethanol (10.1g) in THF (50ml) is added 4,5-dimethylthiazole (14.8g) also in THF (100ml) and then, dropwise, triethylamine (10.1g). Stir at 50°C for 4 hours. Cool to room temperature and filter out the solid. Evaporate the solvent and dissolve the crude product in 10ml of methylene chloride. Pass through a silica plug (100g) in a fritted filter funnel, and elute with methanol/methylene chloride (10:90), applying suction until the product has been collected. The yield of (R)-1-(4,5-dimethyl-2-thiazolyl)-2-hydroxymethylpyrrolidine is 19.5g.

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Example 4- 2-chloropyridine (12g) and 2-(methylamino)ethanol (100ml) are stirred under nitrogen at 120°C for 18 hours. Cool to room temperature and then pour into iced water (250ml). Extract with ethyl acetate (2x200ml). Dry over sodium sulfate. Filter. Evaporate to dryness. The crude product is distilled in vacuo to give 10.3g of N-methyl-N-(2-pyridinyl)-2-aminoethanol, boiling at 110°C/1.0mmHg.

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Example 5- A solution of 2-chlorobenzoxazole (15.3g) in THF (100ml) is added dropwise to an ice-cold solution of 2-(methylamino)ethanol (8.0g) and triethylamine (10.1g) also in THF (100ml). The mixture is stirred at room temperature for 4 hours and the solid is filtered off. The solvent is evaporated and the residue is dissolved in methylene chloride and passed through a silica plug (100g), eluting with

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methanol/methylene chloride (10:90) until the product has been collected. The yield of N-methyl-N-(2-benzoxazolyl)-2-aminoethanol is 15.7g.

Example 6- Thionyl chloride (2.5ml) was added dropwise to an ice-cold solution of  
5 (R)-6-hydroxy-2,5,7,8-tetramethylchroman-2-ylcarbinol (5.1g) in anhydrous methylene chloride (50ml). The solution was stirred at 0°C for 1 hour and then at room temperature for another period of 2 hours. Wash with saturated sodium bicarbonate solution (2x25ml), then with brine (25ml), and then with water (25ml). Dry over sodium sulfate, filter, and evaporate to dryness. The crude product, (R)-6-  
10 hydroxy-2,5,7,8-tetramethylchroman-2-ylmethyl chloride (5.2g) is used as is in the next step.

Example 7- Thionyl chloride (2.5ml) was added dropwise to an ice-cold solution of  
15 (S)-6-hydroxy-2,5,7,8-tetramethylchroman-2-ylcarbinol (5.1g) in anhydrous methylene chloride (50ml). The solution was stirred at 0°C for 1 hour and then at room temperature for another period of 2 hours. Wash with saturated sodium bicarbonate solution (2x25ml), then with brine (25ml), and then with water (25ml). Dry over sodium sulfate, filter, and evaporate to dryness. The crude product, (S)-6-  
20 hydroxy-2,5,7,8-tetramethylchroman-2-ylmethyl chloride (5.0g) is used as is in the next step.

Example 8- A mixture of (R)-6-hydroxy-2,5,7,8-tetramethylchroman-2-ylmethyl chloride (8.43g), triethylamine (2.6g), and 2-(methylamino)ethanol (40ml) is stirred at  
25 120°C under nitrogen for 16 hours. Cool to room temperature and pour into iced water (100ml). Extract with ethyl acetate (3x100ml) and wash the combined organic extracts with brine (100ml). Dry over sodium sulfate. Filter. Evaporate to dryness. The product, (R)-2-[N-(6-hydroxy-2,5,7,8-tetramethylchroman-2-ylmethyl)-N-methylamino]ethanol weighs 9.0g.

30 Example 9- A mixture of (S)-6-hydroxy-2,5,7,8-tetramethylchroman-2-ylmethyl chloride (8.43g), triethylamine (2.6g), and 2-(methylamino)ethanol (40ml) is stirred at 120°C under nitrogen for 16 hours. Cool to room temperature and pour into iced water (100ml). Extract with ethyl acetate (3x100ml) and wash the combined organic

extracts with brine (100ml). Dry over sodium sulfate. Filter. Evaporate to dryness. The product, (S)-2-[N-(6-hydroxy-2,5,7,8-tetramethylchroman-2-ylmethyl)-N-methylamino]ethanol weighs 8.9g.

- 5 Example 10- A mixture of 2-chlorobenzoxazole (3.7g), (L)-proline methyl ester, hydrochloride salt (4.0g), and triethylamine (4.9g) in anhydrous THF (50ml) is stirred at room temperature for 18 hours. The solid is filtered off and washed with THF (10ml). The solution is evaporated to dryness and the crude product is dissolved in methylene chloride (5ml) and passed through a plug of silica (50g), eluting with ethyl acetate/methylene chloride (10:90). The product, (L)-N-(2-benzoxazolyl)-proline methyl ester (5.0g) is a crystalline solid.

- 15 Example 11- A mixture of 2-chlorobenzoxazole (3.7g), (D)-proline methyl ester, hydrochloride salt (4.0g), and triethylamine (4.9g) in anhydrous THF (50ml) is stirred at room temperature for 18 hours. The solid is filtered off and washed with THF (10ml). The solution is evaporated to dryness and the crude product is dissolved in methylene chloride (5ml) and passed through a plug of silica (50g), eluting with ethyl acetate/methylene chloride (10:90). The product, (D)-N-(2-benzoxazolyl)-proline methyl ester (5.5g) is a crystalline solid.

- 20 Example 12- (L)-N-(2-benzoxazolyl)-proline methyl ester (5.0g) is suspended in a mixture consisting of methanol (50ml), water (5ml), and lithium hydroxide (0.5g). Stir for 18 hours at room temperature. Acidify to pH 4.5 with citric acid. Extract with ethyl acetate (4x50ml). Dry over sodium sulfate, filter, and evaporate to dryness. The product, (L)-N-(2-benzoxazolyl)-proline (4.3g) is an off-white solid.

- 30 Example 13- A mixture of (L)-proline (4.6g), 2-chlorobenzoxazole (6.6g), and triethylamine (4.45g) in anhydrous THF (100ml) is stirred at reflux temperature for 18 hours. Cool down to room temperature, filter off the solid and wash it with a THF (10ml). Evaporate the solvent. Add ethyl acetate (50ml) and then 1N sodium hydroxide (50ml). Stir for 5 minutes. Keep the aqueous phase. Wash again with ethyl acetate (50ml). Acidify with citric acid to pH 4.5. Isolate the precipitate by filtration. The aqueous filtrate is extracted with ethyl acetate (4x30ml). Dry over

sodium sulfate. Filter. Evaporate to dryness. The solids are dried in vacuo at 35°C for 18 hours. The first crop of product weighs 4.77g. The second crop weighs 3.26g. The total amount of product, (L)-N-(2-benzoxazolyl)-proline, is 8.03g.

5 Example 14- A mixture of (D)-proline (4.6g), 2-chlorobenzoxazole (6.6g), and triethylamine (4.45g) in anhydrous THF (100ml) is stirred at reflux temperature for 18 hours. Cool down to room temperature, filter off the solid and wash it with a THF (10ml). Evaporate the solvent. Add ethyl acetate (50ml) and then 1N sodium hydroxide (50ml). Stir for 5 minutes. Keep the aqueous phase. Wash again with  
10 ethyl acetate (50ml). Acidify with citric acid to pH 4.5. Isolate the precipitate by filtration. The aqueous filtrate is extracted with ethyl acetate (4x30ml). Dry over sodium sulfate. Filter. Evaporate to dryness. The solids are dried in vacuo at 35°C for 18 hours. The first crop of product weighs 4.93g. The second crop weighs 2.90g. The total amount of product, (L)-N-(2-benzoxazolyl)-proline, is 7.83g.

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Example 15- A mixture of 4-hydroxybenzaldehyde (122.12g), 2,4-thiazolidinedione (117.13g), piperidine (5.11g), and benzoic acid (6.11g) in toluene (1,000ml), is stirred at 80°C for 16 hours. Cool to room temperature and filter off the yellow solid. Wash the solid with methylene chloride (3x100ml) and then with methanol/methylene  
20 chloride (30:70) (2x100ml). Dry in vacuo at 35°C until constant weight. The yield of product, 5-(4-hydroxybenzylidene)-2,4-thiazolidinedione, is 217.8g.

Example 16- To p-anisidine (25g) in acetone (400ml) at between 0 and 5°C, add dropwise a solution of sodium nitrite (15.41g) in water (50ml) and 12N hydrochloric  
25 acid (50ml) from 2 different funnels over a 15-minute period. Stir for another 5 minutes at 0°C. Add methyl acrylate (104.9g) and then warm up the solution to 35°C. Transfer into a 2-L Erlenmeyer flask and stir vigorously. While stirring, add copper(I) oxide (0.7g) in several portions. Keep stirring for as long as nitrogen gas evolves from the solution, then stir for another 4 hours. Evaporate the organic solvent  
30 and dilute the aqueous residue with water (200ml). Extract with methylene chloride (200ml). Dry over sodium sulfate, filter, and evaporate to dryness. The product, methyl 2-chloro-3-(4-methoxyphenyl)propanoate, is a dark oil weighing 42.96g.



Example 17- Methyl 2-chloro-3-(4-methoxyphenyl)propanoate (31.44g), thiourea (16.89g), and anhydrous sodium acetate (11.24g) in 2-methoxyethanol (100ml) is stirred at 100°C for 4 hours. Cool to room temperature and place the flask at 4°C for 16 hours. The pale yellow solid is filtered off and is washed with hexanes (50ml).  
5 Stir for 30 minutes in ethyl acetate/water (100ml:10ml). Filter. Crystallize from hot ethanol (600ml). After leaving at 4°C for 16 hours, the crystals are filtered off and stirred at reflux for 8 hours in a mixture of 2-methoxyethanol (100ml) and 2N hydrochloric acid (20ml). Evaporate the solvent. Add ethyl acetate (200ml) and water (200ml). Keep the organic phase and wash again with water (200ml). Dry over  
10 sodium sulfate, filter, evaporate to dryness. The product, 5-(4-methoxybenzyl)thiazolidine-2,4-dione (16.7g) is an oil that solidifies upon standing.

Example 18- To a solution of 5-(4-methoxybenzyl)thiazolidine-2,4-dione (14.3g) in anhydrous methylene chloride (100ml) cooled to -40°C, add a 1.0M solution of boron  
15 tribromide in methylene chloride (63ml). The solution is left to warm up to 23°C and is then stirred for another 16 hours. Pour into iced water (700ml) and stir for 15 minutes. Isolate the precipitate by filtration. Wash the product with water (50ml) and then with methylene chloride (50ml). The yield of 5-(4-hydroxybenzyl)thiazolidine-2,4-dione is 12.8g.

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Example 19- A mixture of methyl 4-formylbenzoate (164.16g), 2,4-thiazolidinedione (117.13g), piperidine (5.11g), and benzoic acid (6.11g) in toluene (1,000ml), is stirred at 80°C for 16 hours. Cool to room temperature and filter off the yellow solid. Wash the solid with methylene chloride (3x100ml) and then with methanol/methylene  
25 chloride (30:70) (2x100ml). Dry in vacuo at 35°C until constant weight. The yield of product, 5-(4-carbomethoxybenzylidene)-2,4-thiazolidinedione, is 258.0g.

Example 20- A suspension of 5-(4-carbomethoxybenzylidene)-2,4-thiazolidinedione (26.3g) and magnesium turnings (24g) in anhydrous methanol (300ml) is stirred at  
30 45°C for 8 hours. Acidify to pH 5.0 with 6N HCl and then extract with methylene chloride (2x250ml). Dry over sodium sulfate, filter, and evaporate to dryness. The crude product is chromatographed on silica gel (1,300g), eluting with

methanol/methylene chloride (02:98). The yield of 5-(4-carbomethoxybenzyl)-2,4-thiazolidinedione is 15.2g.

5 Example 21- A suspension of 5-(4-carbomethoxybenzylidene)-2,4-thiazolidinedione (50g) in 6N HCl (200ml) is stirred at reflux for 4 hours. The mixture is cooled to 4°C and the product is filtered off. The product is then washed with water (2x100ml) and is dried in vacuo at 40°C. The yield of 5-(4-carboxybenzylidene)-2,4-thiazolidinedione is 45g.

10 Example 22- A suspension of 5-(4-carbomethoxybenzyl)-2,4-thiazolidinedione (50g) in 6N HCl (200ml) is stirred at reflux for 4 hours. The mixture is cooled to 4°C and the product is filtered off. The product is then washed with water (2x100ml) and is dried in vacuo at 40°C. The yield of 5-(4-carboxybenzyl)-2,4-thiazolidinedione is 44g.

15 Example 23- (R)-6-Hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid (9.2g) and 5-(4-hydroxybenzyl)thiazolidine-2,4-dione (8.3g) are dissolved in methylene chloride (100ml) and THF (50ml). To this add dicyclohexylcarbodiimide (7.6g) and DMAP (0.5g), and then stir for 4 hours at room temperature. The solid is removed by  
20 filtration and is washed with a small amount of THF (20ml). The solvent is removed and the solid residue is stirred with methylene chloride (100ml) and left at 4°C for 16 hours. The product is isolated by filtration and dried in vacuo at 23°C. The yield of 5-{4-[(R)-6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxy]benzyl}thiazolidine-2,4-dione is 12.4g.

25 Example 24- (S)-6-Hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid (9.2g) and 5-(4-hydroxybenzyl)thiazolidine-2,4-dione (8.3g) are dissolved in methylene chloride (100ml) and THF (50ml). To this add dicyclohexylcarbodiimide (7.6g) and DMAP (0.5g), and then stir for 4 hours at room temperature. The solid is removed by  
30 filtration and is washed with a small amount of THF (20ml). The solvent is removed and the solid residue is stirred with methylene chloride (100ml) and left at 4°C for 16 hours. The product is isolated by filtration and dried in vacuo at 23°C. The yield of

5-{4-[(S)-6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxy]benzyl}thiazolidine-2,4-dione is 13.3g.

Example 25- (R)-6-Hydroxy-2,5,7,8-tetramethylchroman-2-carbinol (1.9g) and 5-(4-carboxybenzyl)thiazolidine-2,4-dione (1.8g) are dissolved in methylene chloride (20ml) and THF (10ml). To this add dicyclohexylcarbodiimide (1.6g) and DMAP (0.1g), and then stir for 4 hours at room temperature. The solid is removed by filtration and is washed with a small amount of THF (5ml). The solvent is removed and the solid residue is stirred with methylene chloride (20ml) and left at 4°C for 16 hours. The product is isolated by filtration and dried in vacuo at 23°C. The yield of 5-{4-[(R)-6-hydroxy-2,5,7,8-tetramethylchroman-2-methoxy]benzyl}thiazolidine-2,4-dione is 2.54g.

Example 26- (S)-6-Hydroxy-2,5,7,8-tetramethylchroman-2-carbinol (1.9g) and 5-(4-carboxybenzyl)thiazolidine-2,4-dione (1.8g) are dissolved in methylene chloride (20ml) and THF (10ml). To this add dicyclohexylcarbodiimide (1.6g) and DMAP (0.1g), and then stir for 4 hours at room temperature. The solid is removed by filtration and is washed with a small amount of THF (5ml). The solvent is removed and the solid residue is stirred with methylene chloride (20ml) and left at 4°C for 16 hours. The product is isolated by filtration and dried in vacuo at 23°C. The yield of 5-{4-[(S)-6-hydroxy-2,5,7,8-tetramethylchroman-2-methoxy]benzyl}thiazolidine-2,4-dione is 2.17g.

Example 27- (R)-6-Hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid (4.6g) and 5-(4-hydroxybenzylidene)thiazolidine-2,4-dione (4.2g) are dissolved in methylene chloride (50ml) and THF (25ml). To this add dicyclohexylcarbodiimide (3.8g) and DMAP (0.25g), and then stir for 4 hours at room temperature. The solid is removed by filtration and is washed with a small amount of THF (10ml). The solvent is removed and the solid residue is stirred with methylene chloride (50ml) and left at 4°C for 16 hours. The product is isolated by filtration and dried in vacuo at 23°C. The yield of 5-{4-[(R)-6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxy]benzylidene}thiazolidine-2,4-dione is 5.9g.

Example 28- (S)-6-Hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid (4.6g) and 5-(4-hydroxybenzylidene)thiazolidine-2,4-dione (4.2g) are dissolved in methylene chloride (50ml) and THF (25ml). To this add dicyclohexylcarbodiimide (3.8g) and DMAP (0.25g), and then stir for 4 hours at room temperature. The solid is removed by filtration and is washed with a small amount of THF (10ml). The solvent is removed and the solid residue is stirred with methylene chloride (50ml) and left at 4°C for 16 hours. The product is isolated by filtration and dried in vacuo at 23°C. The yield of 5-{4-[(S)-6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxy]benzylidene}thiazolidine-2,4-dione is 6.2g.

Example 29- (R)-6-Hydroxy-2,5,7,8-tetramethylchroman-2-carbinol (3.8g) and 5-(4-carboxybenzylidene)thiazolidine-2,4-dione (3.6g) are dissolved in methylene chloride (40ml) and THF (20ml). To this add dicyclohexylcarbodiimide (3.2g) and DMAP (0.2g), and then stir for 4 hours at room temperature. The solid is removed by filtration and is washed with a small amount of THF (10ml). The solvent is removed and the solid residue is stirred with methylene chloride (40ml) and left at 4°C for 16 hours. The product is isolated by filtration and dried in vacuo at 23°C. The yield of 5-{4-[(R)-6-hydroxy-2,5,7,8-tetramethylchroman-2-methoxy]benzylidene}thiazolidine-2,4-dione is 5.4g.

Example 30- (S)-6-Hydroxy-2,5,7,8-tetramethylchroman-2-carbinol (3.8g) and 5-(4-carboxybenzylidene)thiazolidine-2,4-dione (3.6g) are dissolved in methylene chloride (40ml) and THF (20ml). To this add dicyclohexylcarbodiimide (3.2g) and DMAP (0.2g), and then stir for 4 hours at room temperature. The solid is removed by filtration and is washed with a small amount of THF (10ml). The solvent is removed and the solid residue is stirred with methylene chloride (40ml) and left at 4°C for 16 hours. The product is isolated by filtration and dried in vacuo at 23°C. The yield of 5-{4-[(S)-6-hydroxy-2,5,7,8-tetramethylchroman-2-methoxy]benzylidene}thiazolidine-2,4-dione is 5.2g.

Example 31- (L)-N-(2-benzoxazolyl)-proline (3.26g) and 5-(4-hydroxybenzyl)thiazolidine-2,4-dione (3.11g) are suspended in methylene chloride (100ml). Add DCC (2.89g) and DMAP (0.12g) and stir at room temperature for 4

hours. Filter and purify on 114g of silica, eluting with methanol/methylene chloride (02:98). The yield of 5-{4-[(S)-1-(2-benzoxazolyl)pyrrolidine-2-carboxy]benzyl}thiazolidine-2,4-dione is 4.55g.

5 Example 32- (L)-1-(2-benzoxazolyl)pyrrolidine-2-carbinol (3.26g) and 5-(4-carboxybenzyl)thiazolidine-2,4-dione (3.25g) are suspended in methylene chloride (100ml). Add DCC (2.88g) and DMAP (0.12g) and stir at room temperature for 4 hours. Filter and purify on 132g of silica, eluting with methanol/methylene chloride (02:98). The yield of 5-{4-[(S)-1-(2-benzoxazolyl)pyrrolidinyl-2-methoxycarbonyl]benzyl}-thiazolidine-2,4-dione is 4.68g.

15 Example 33- (D)-1-(2-benzoxazolyl)pyrrolidine-2-carbinol (3.26g) and 5-(4-carboxybenzylidene)thiazolidine-2,4-dione (3.35g) are suspended in methylene chloride (100ml). Add DCC (2.91g) and DMAP (0.12g) and stir at room temperature for 4 hours. Filter and purify on 108g of silica, eluting with methanol/methylene chloride (02:98). The yield of 5-{4-[(R)-1-(2-benzoxazolyl)pyrrolidinyl-2-methoxycarbonyl]benzylidene}-thiazolidine-2,4-dione is 4.32g.

20 Example 34- (D)-1-(2-benzoxazolyl)pyrrolidine-2-carbinol (3.26g) and 5-(4-carboxybenzyl)thiazolidine-2,4-dione (3.25g) are suspended in methylene chloride (100ml). Add DCC (2.93g) and DMAP (0.12g) and stir at room temperature for 4 hours. Filter and purify on 162g of silica, eluting with methanol/methylene chloride (02:98). The yield of 5-{4-[(S)-1-(2-benzoxazolyl)pyrrolidinyl-2-methoxycarbonyl]benzyl}-thiazolidine-2,4-dione is 4.77g.

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Example 35- Triethylamine (8.3ml) is added dropwise to a stirred cold solution of ethyl 2-aminoacetoacetate hydrochloride (5.4g) and 4-methoxybenzoyl chloride (5.2g) in dichloromethane (100ml). After stirring for 3 hours, the solution is washed with water (100ml), dried over sodium sulfate, filtered, and evaporated to dryness.

30 The crude product, ethyl 2-(4-methoxy)phenylaminoacetoacetate weighs 6.7g.

Example 36- Ethyl 2-(4-methoxy)phenylaminoacetoacetate (5.9g) and phosphorus oxychloride (50ml) are stirred at 100C for 30 minutes. The phosphorus oxychloride is

removed by evaporation, and the residue is diluted with aqueous sodium bicarbonate and extracted with methylene chloride. After drying over sodium sulfate, the solution is evaporated and the product is crystallized from hexane, giving ethyl 5-methyl-2-(4-methoxy)phenyl-4-oxazolecarboxylate (4.5g).

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Example 37- A solution of benzoyl chloride (17g) in ethyl acetate (40ml) is added dropwise, with stirring, in an ice-cold mixture of L-serine methyl ester, hydrochloride (15.5g), water (100ml), sodium bicarbonate (21.8g), and ethyl acetate (100ml). After stirring for 2 hours, the organic phase is separated, dried over sodium sulfate, and  
10 evaporated to give crystalline N-benzoyl-L-serine methyl ester (22.0g).

Example 38- A stirred mixture of N-benzoyl-L-serine methyl ester (21.0g), thionyl chloride (21.0g), and methylene chloride (150ml) is stirred at reflux for 1 hour. The solvent is evaporated and the residue is diluted with cold water. Neutralize with  
15 sodium bicarbonate, and extract with ethyl acetate. Purification on silica gel (250g), eluting with methanol:methylene chloride (01:99), yields methyl (S)-2-phenyl-2-oxazoline-4-carboxylate (15.2g).

Example 39- A solution of benzoyl chloride (17g) in ethyl acetate (40ml) is added  
20 dropwise, with stirring, in an ice-cold mixture of L-threonine methyl ester, hydrochloride (16.5g), water (100ml), sodium bicarbonate (21.8g), and ethyl acetate (100ml). After stirring for 2 hours, the organic phase is separated, dried over sodium sulfate, and evaporated to give crystalline N-benzoyl-L-threonine methyl ester (21.5g).

25

Example 40- A stirred mixture of N-benzoyl-L-threonine methyl ester (21.0g), thionyl chloride (21.0g), and methylene chloride (150ml) is stirred at reflux for 1 hour. The solvent is evaporated and the residue is diluted with cold water. Neutralize with sodium bicarbonate, and extract with ethyl acetate. Purification on silica gel (250g),  
30 eluting with methanol:methylene chloride (01:99), yields methyl (R,S)-2-phenyl-2-oxazoline-5-methyl-4-carboxylate (14.8g).

Example 41- Activity in NIDDM KK-A<sup>y</sup> male mice. Non-insulin dependent diabetic mellitus male mice, weighing 50 +/- 5g (9-10 weeks of age) were used. These animals exhibited hyperinsulinemia, hyperglycemia, and islet atrophy. The test compounds **105**, **115**, and **155**, and the positive control compound **troglitazone** were  
5 suspended in a 1% carboxymethylcellulose preparation and were given orally at a dose of 10mg/kg, twice a day, for 5 consecutive days. Blood sampling was performed before the first dose and then 90 minutes after the last dose. Serum glucose and insulin levels were measured. Percent reduction of serum glucose and insulin levels relative to the pre-treatment values are shown in Table XXIII and Figures 19 and 20.

10

It should be understood that the reaction schemes and embodiments described herein are for illustrative purposes only and that various modifications or changes in light thereof will be suggested to persons skilled in the art and are to be included within the spirit and purview of this application and the scope of the appended claims.

Formula I

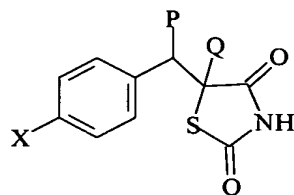
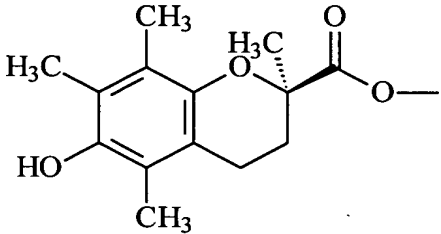
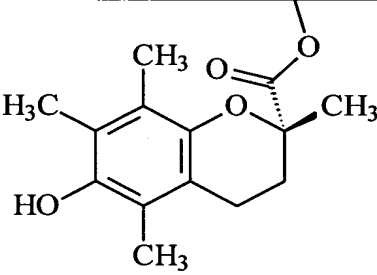
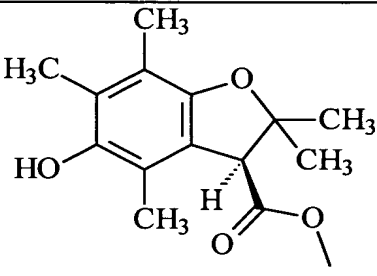
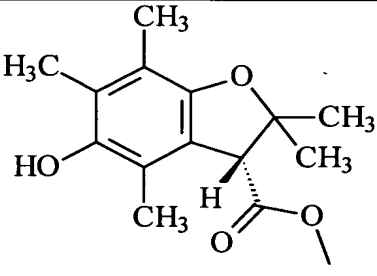


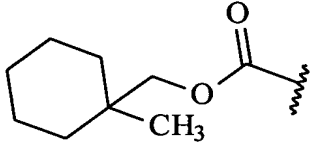
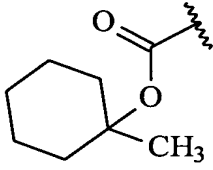
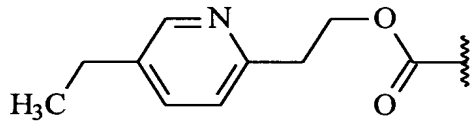
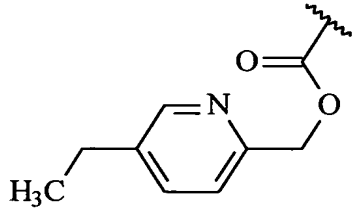
Table I.

Compound number	X	P and Q*
1		H
2		db
3		H
4		db
5		H
6		db
7		H
8		db



Table I (continued).

Compound number	X	P and Q*
9		H
10		db
11		H
12		db
13		H
14		db
15		H
16		db

Compound number	X	P and Q*
17		H
18		db
19		H
20		db
21		H
22		db
23		H
24		db

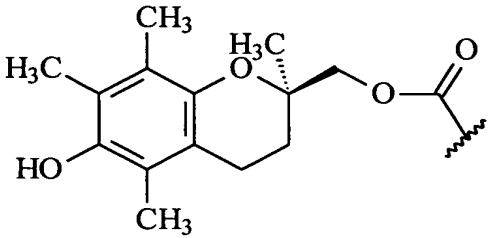
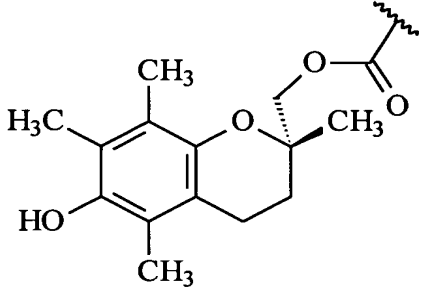
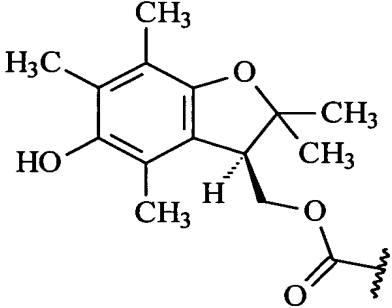
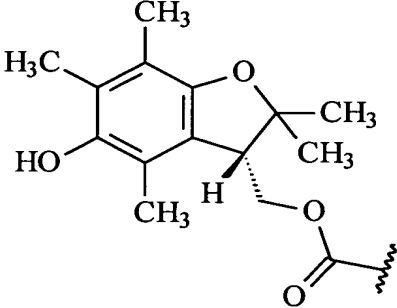
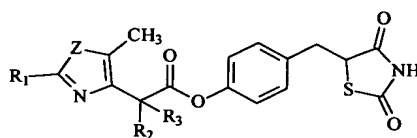
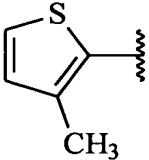
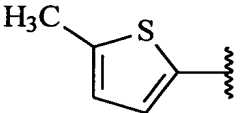
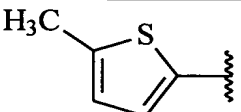
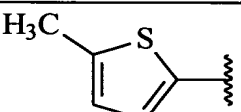
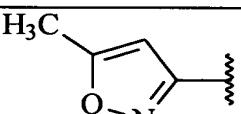
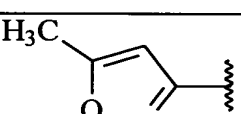
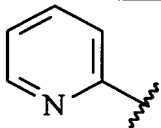
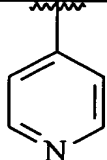
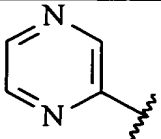
Compound number	X	P and Q*
25		H
26		db
27		H
28		db
29		H
30		db
31		H
32		db

Table II.

Formula II



Compound number	Z	R1	R2	R3
33	O		H	H
34	O		CH3	H
35	O		CH3	CH3
36	S		CH3	H
37	O		CH3	H
38	S		CH3	H
39	O		CH3	H
40	S		CH3	H
41	O		CH3	H

Compound number	Z	R1	R2	R3
42	S		CH3	H
43	O		H	H
44	O		CH3	H
45	S		H	H
46	O		CH3	H
47	S		H	H
48	O		CH3	H
49	O		CH3	H
50	O		CH3	H

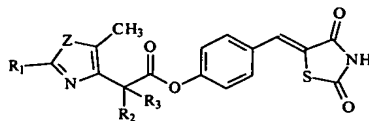


Table III.

Compound number	Z	R1	R2	R3
51	O		H	H
52	O		CH3	H
53	O		CH3	CH3
54	S		CH3	H
55	O		CH3	H
56	S		CH3	H
57	O		CH3	H
58	S		CH3	H
59	O		CH3	H

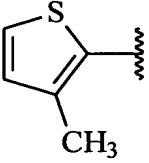
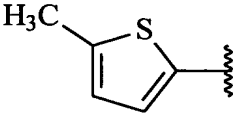
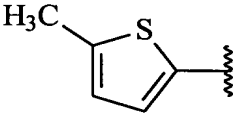
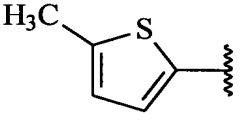
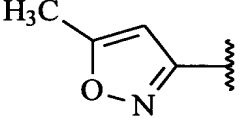
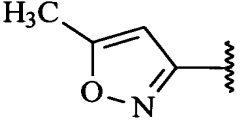
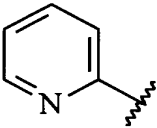
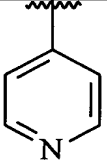
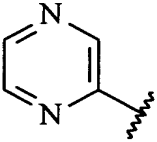
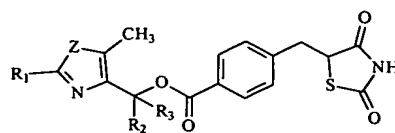
Compound number	Z	R1	R2	R3
60	S		CH3	H
61	O		H	H
62	O		CH3	H
63	S		H	H
64	O		CH3	H
65	S		H	H
66	O		CH3	H
67	O		CH3	H
68	O		CH3	H

Table IV.



Compound number	Z	R1	R2	R3
69	O		H	H
70	O		CH3	H
71	O		CH3	CH3
72	S		CH3	H
73	O		CH3	H
74	S		CH3	H
75	O		CH3	H
76	S		CH3	H
77	O		CH3	H



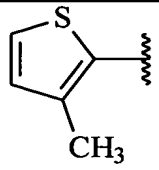
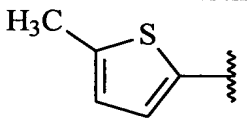
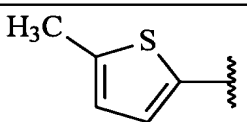
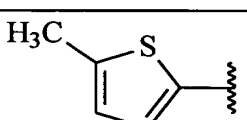
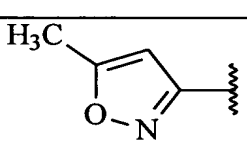
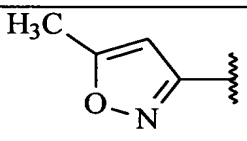
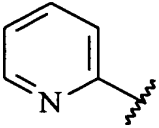
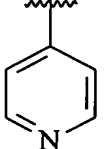
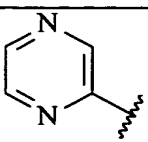
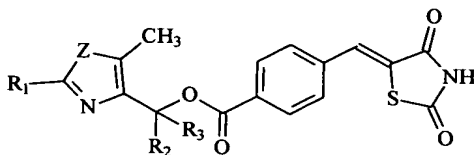
Compound number	Z	R1	R2	R3
78	S		CH3	H
79	O		H	H
80	O		CH3	H
81	S		H	H
82	O		CH3	H
83	S		H	H
84	O		CH3	H
85	O		CH3	H
86	O		CH3	H

Table V.



Compound number	Z	R1	R2	R3
87	O		H	H
88	O		CH3	H
89	O		CH3	CH3
90	S		CH3	H
91	O		CH3	H
92	S		CH3	H
93	O		CH3	H
94	S		CH3	H
95	O		CH3	H

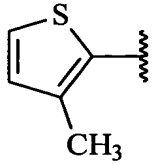
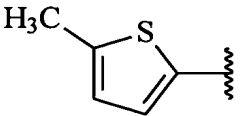
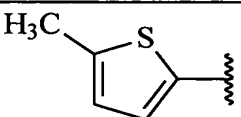
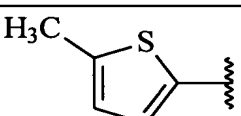
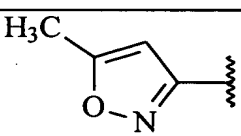
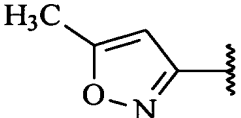
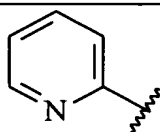
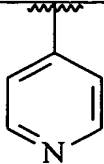
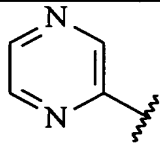
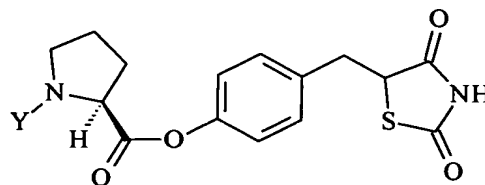
Compound number	Z	R1	R2	R3
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97	O		H	H
98	O		CH3	H
99	S		H	H
100	O		CH3	H
101	S		H	H
102	O		CH3	H
103	O		CH3	H
104	O		CH3	H

Table VI.



Compound number	Y
105	
106	
107	
108	
109	

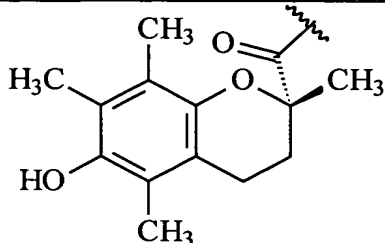
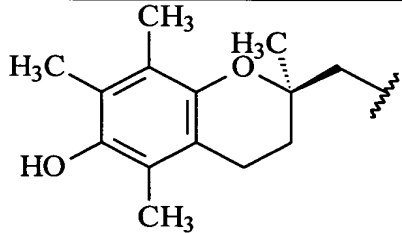
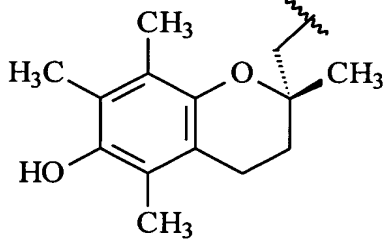
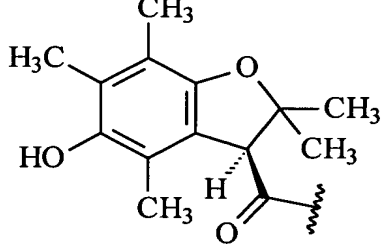
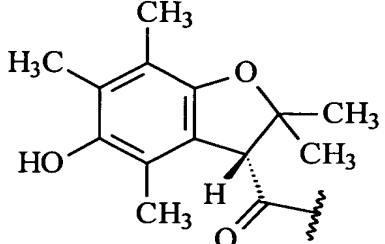
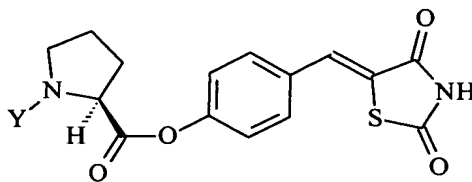
Compound number	Y
110	
111	
112	
113	
114	

Table VII.



Compound number	Y
115	
116	
117	
118	
119	

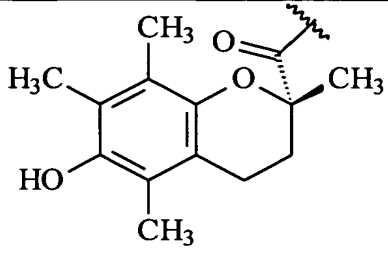
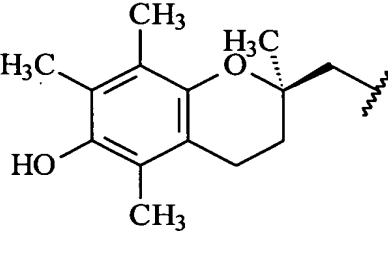
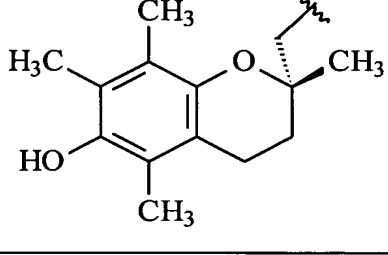
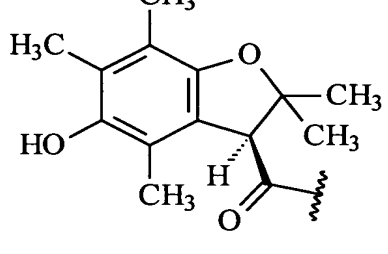
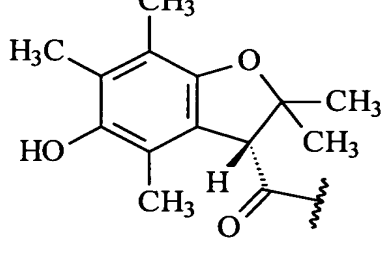
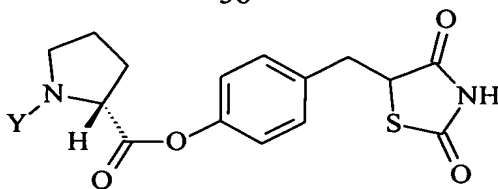
Compound number	Y
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121	
122	
123	
124	

Table VIII.



Compound number	Y
125	
126	
127	
128	
129	



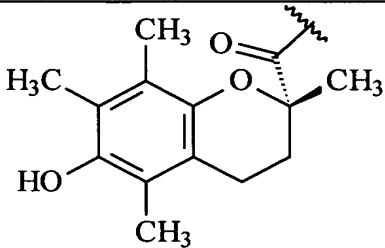
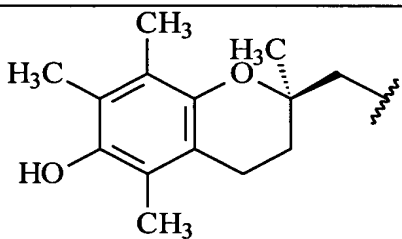
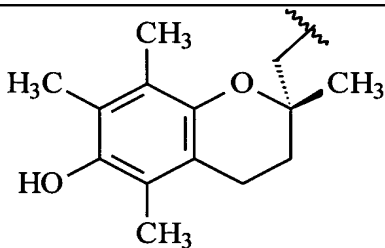
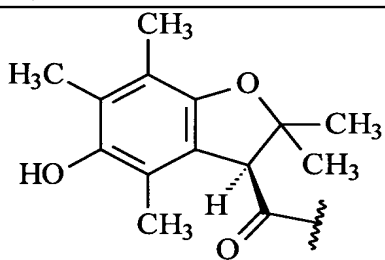
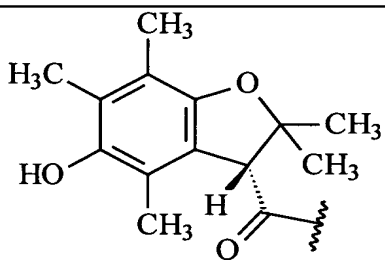
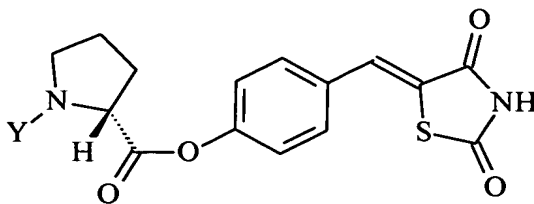
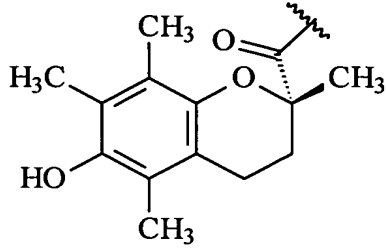
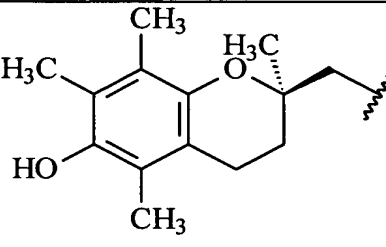
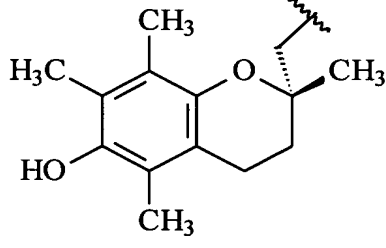
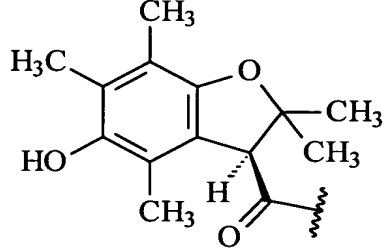
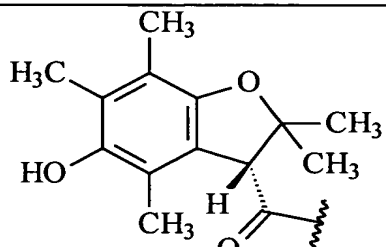
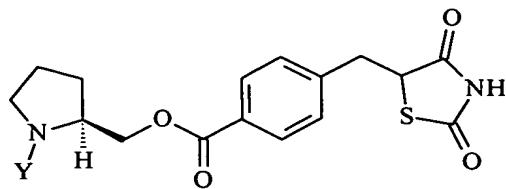
Compound number	Y
130	
131	
132	
133	
134	

Table IX.



Compound number	Y
135	
136	
137	
138	
139	

Compound number	Y
140	
141	
142	
143	
144	

**Table X.**

Compound number	Y
145	
146	
147	
148	
149	

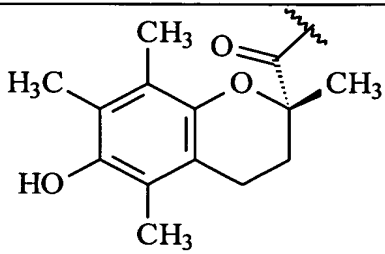
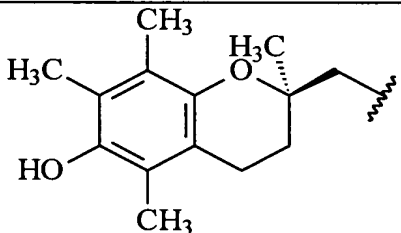
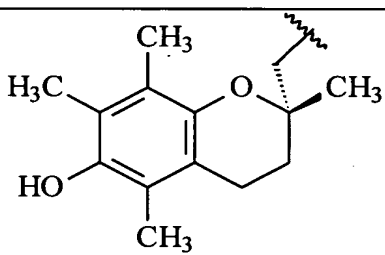
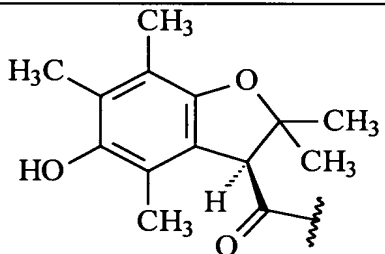
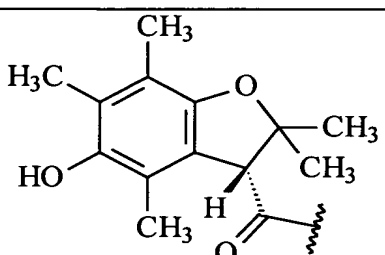
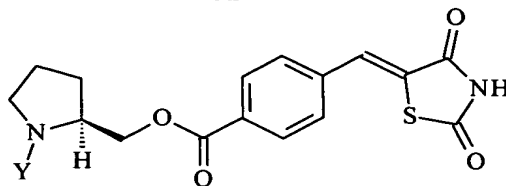
Compound number	Y
150	
151	
152	
153	
154	

Table XI.



Compound number	Y
155	
156	
157	
158	
159	

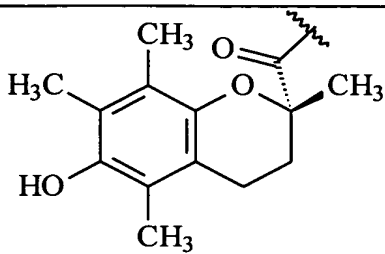
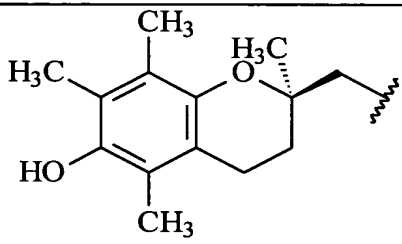
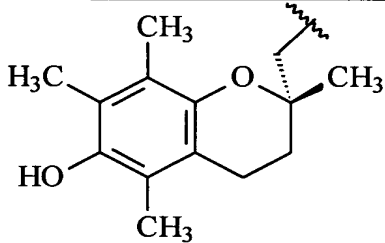
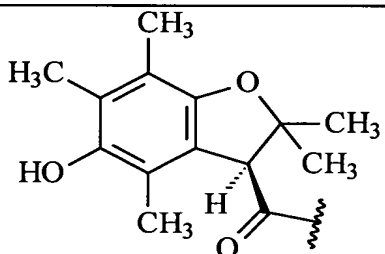
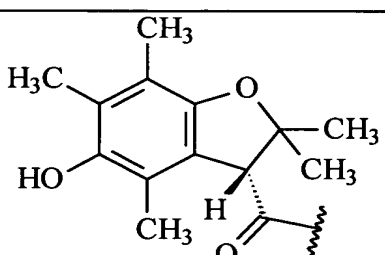
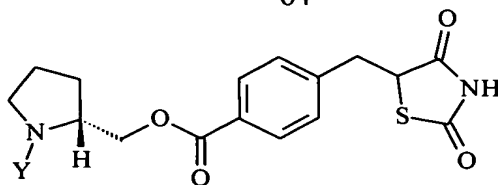
Compound number	Y
160	
161	
162	
163	
164	

Table XII.



Compound number	Y
165	
166	
167	
168	
169	



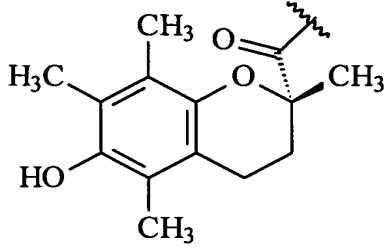
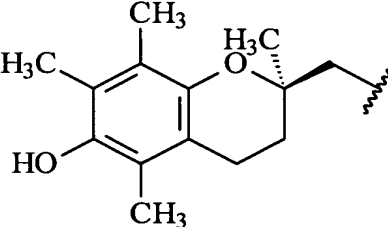
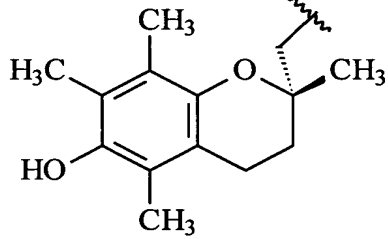
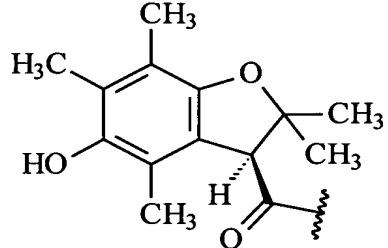
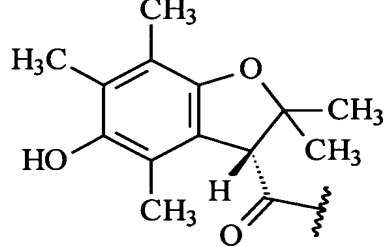
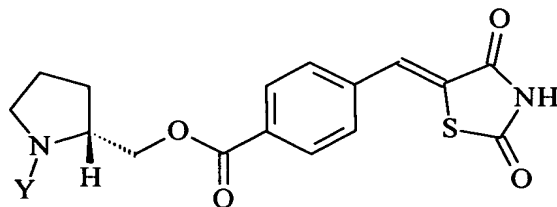
Compound number	Y
170	
171	
172	
173	
174	

Table XIII.



Compound number	Y
175	
176	
177	
178	
179	

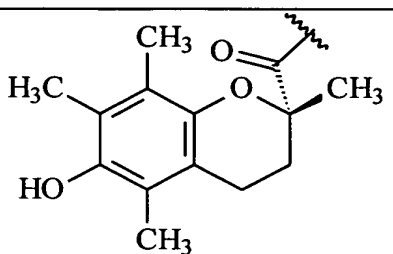
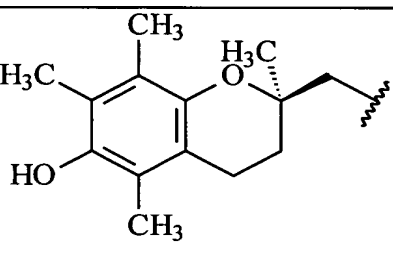
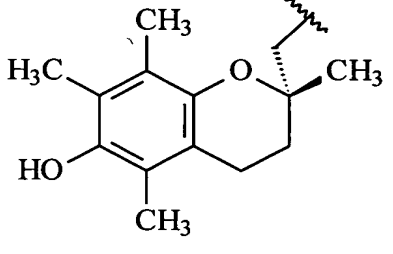
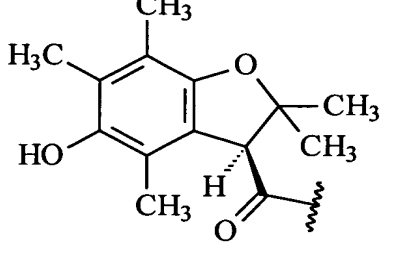
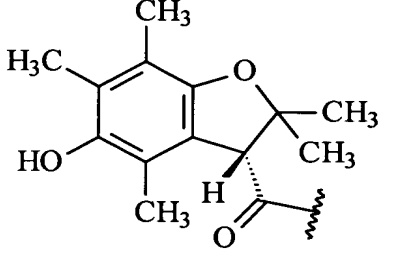
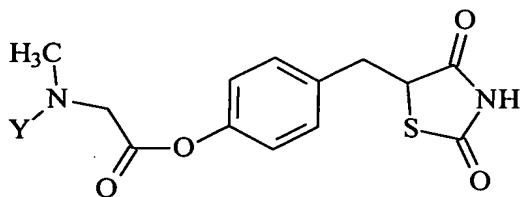
Compound number	Y
180	
181	
182	
183	
184	

Table XIV.



Compound number	Y
185	
186	
187	
188	
189	

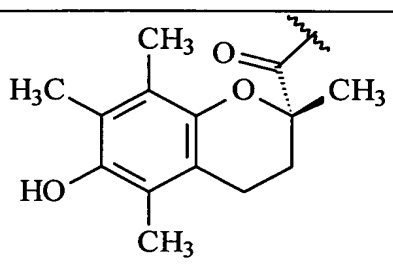
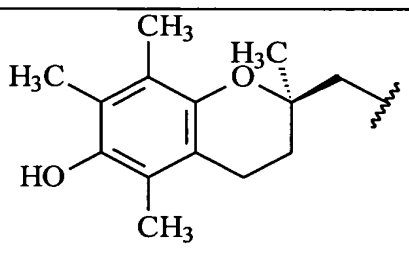
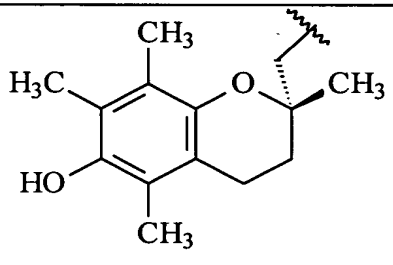
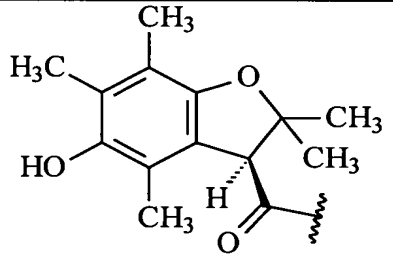
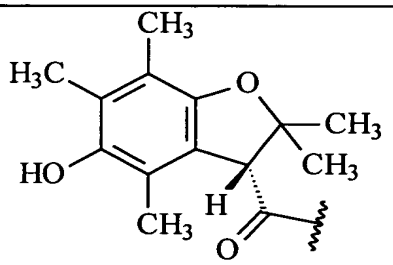
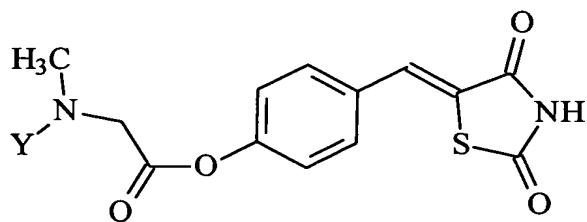
Compound number	Y
190	
191	
192	
193	
194	

Table XV.



Compound number	Y
195	
196	
197	
198	
199	

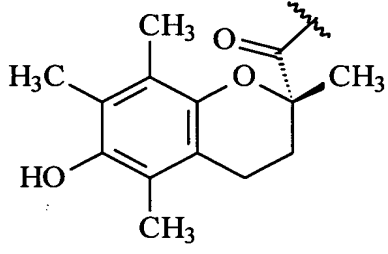
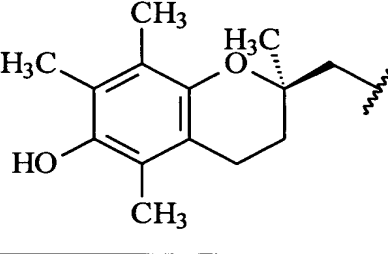
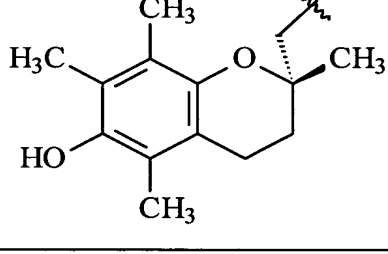
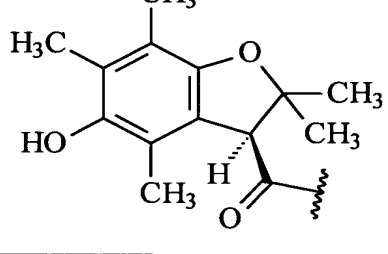
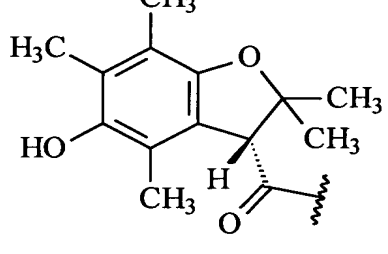
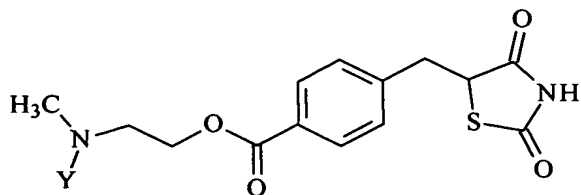
Compound number	Y
200	
201	
202	
203	
204	

Table XVI.



Compound number	Y
205	
206	
207	
208	
209	



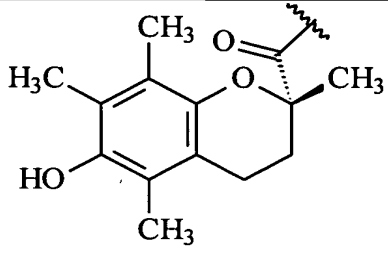
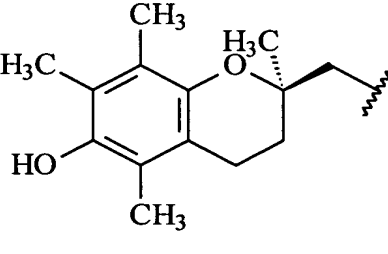
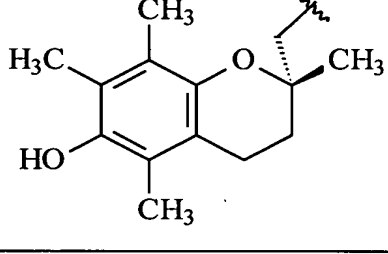
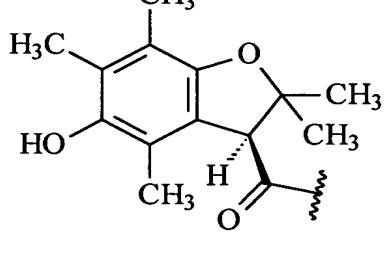
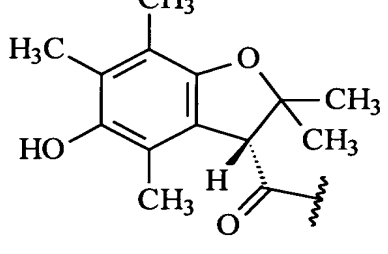
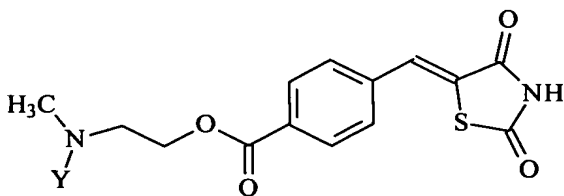
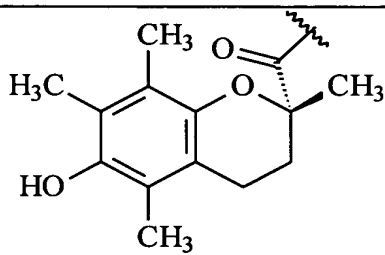
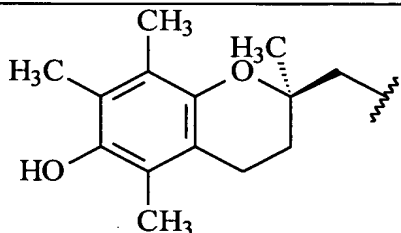
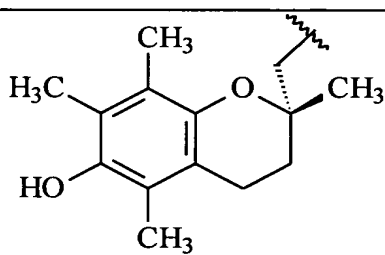
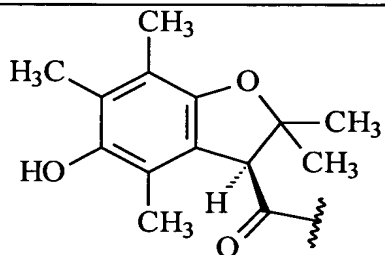
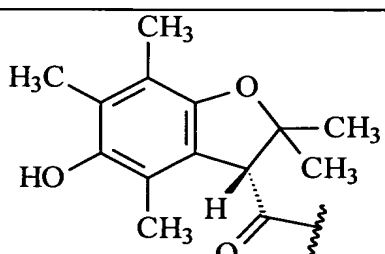
Compound number	Y
210	
211	
212	
213	
214	

Table XVII.



Compound number	Y
215	
216	
217	
218	
219	

Compound number	Y
220	
221	
222	
223	
224	

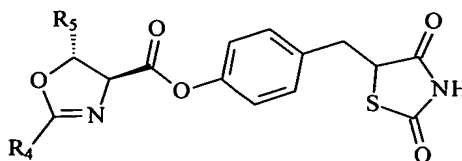
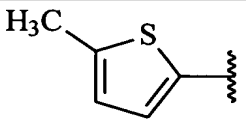
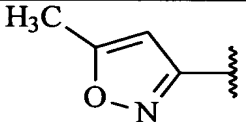
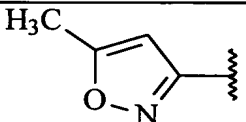
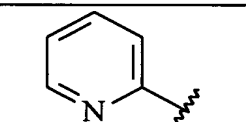
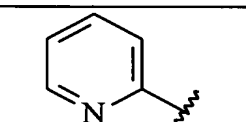
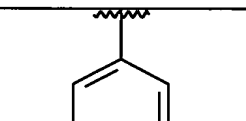
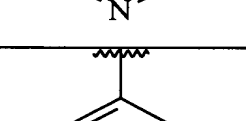
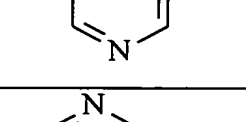
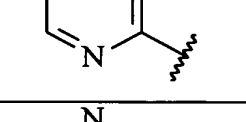


Table XVIII.

Compound number	R4	R5
225		H
226		CH3
227		H
228		CH3
229		H
230		CH3
231		H
232		CH3
233		H

Compound number	R4	R5
234		CH3
235		H
236		CH3
237		H
238		CH3
239		H
240		CH3
241		H
242		CH3

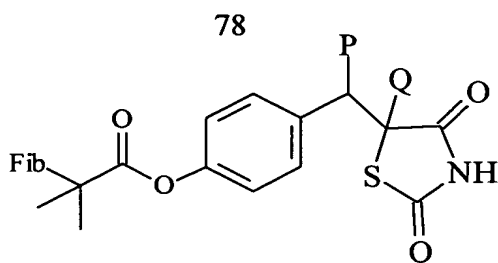
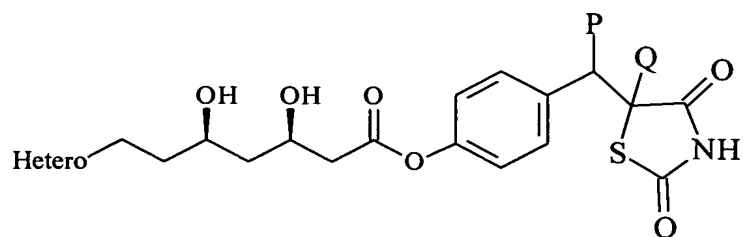
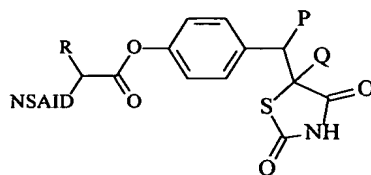


Table XIX.

Compound number	Fib	P and Q*
243		H
244		db
245		H
246		db
247		H
248		db

**Table XX.**

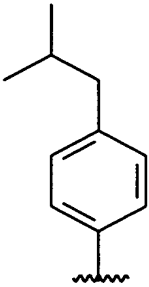
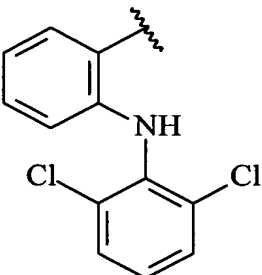
Compound number	Hetero	P and Q*
249		H
250		db
251		H
252		db

**Table XXI**

Compound number	NSAID	P and Q*
253		H
254		db
255		H
256		db



Table XXI (continued)

Compound number	NSAID	P and Q*
257		H
258		db
259		H
260		db

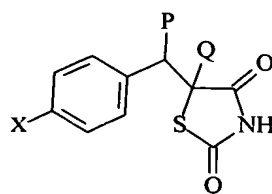


Table XXII

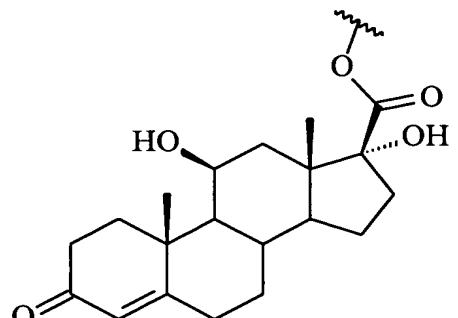
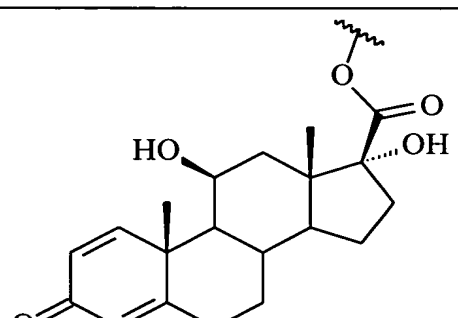
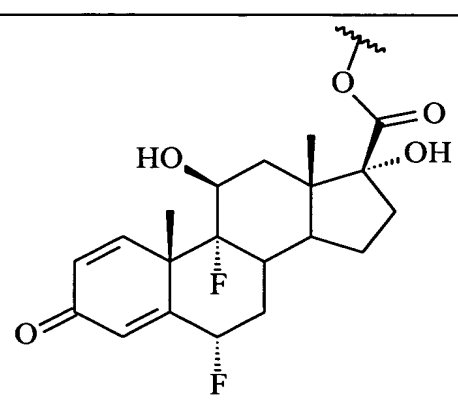
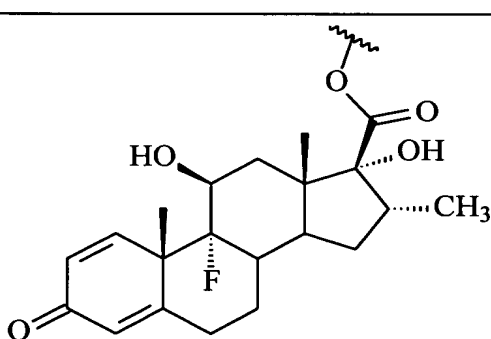
Compound number	X	P and Q*
261		H
262		db
263		H
264		db

Table XXII (continued)

Compound number	X	P and Q*
265		H
266		db
267		H
268		db

**Table XXIII: Activity in NIDDM Mice.**

Compound	Serum Glucose (%)	Serum Insulin (%)
Vehicle	0	1
105	40	10
115	36	13
155	37	9
Troglitazone	35	15